SUB-POPULATION

BRAIN ATLASES

Paul Thompson PhD, Michael S. Mega MD PhD, and Arthur W. Toga PhD

Laboratory of Neuro Imaging, Brain Mapping Division
and Alzheimer's Disease Center
Dept. of Neurology, UCLA School of Medicine, Los Angeles, CA 90095-1769

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Please address correspondence to:
Dr. Paul Thompson
(Rm. 4238, Reed Neurological Research Center)
Laboratory of Neuro Imaging, Dept. of Neurology, UCLA School of Medicine
710 Westwood Plaza, Los Angeles, CA 90095-1769
Phone: (310) 206-2101 **Fax:** (310) 206-5518 **E-mail:** thompson@loni.ucla.edu

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Contents

1. Population-Based Brain Imaging

Recent developments in brain imaging have revolutionized medicine and neuroscience. The ability to image the living brain has greatly accelerated the collection and databasing of brain maps (Mazziotta et al., 1995; Huerta and Koslow, 1996; Fox, 1997; Toga and Thompson, 1998; Letovsky et al., 1998; Van Horn et al., 2001). These maps store information on anatomy and physiology, from whole-brain to molecular scales. Some capture functional changes that occur over milliseconds, and others anatomical changes occurring over entire lifetimes (see e.g. Toga and Mazziotta, 1996; Frackowiak et al., 1997, for recent reviews).

This rapid collection of brain images from healthy and diseased subjects has stimulated the development of mathematical algorithms that compare, pool and average brain data across whole populations. Brain structure is complex, and varies widely from one individual to another. New approaches in computer vision (Bankman, 1999; Fitzpatrick and Sonka, 2000; MacDonald et al., 2000; Xu et al., 1999; Shattuck and Leahy, 2001; Kriegeskorte and Goebel, 2001), anatomical modeling (Thompson et al., 2001; Fischl et al., 2001), differential geometry (Grenander and Miller, 1998; Haker et al., 1999; Hurdal et al., 1999), and statistical field theory (Friston et al., 1995; Worsley et al., 1999; Cao and Worsley, 1999; Taylor and Adler, 2001) are being formulated to capture this variation, encode it, and detect disease-specific patterns (Thompson et al., 1997, 2001). Statistics that describe how brain structure and function vary in a population can greatly empower the analysis of new images (Ashburner et al., 1997; Gee et al., 1998; Dinov et al., 2001; Kang et al., 2001). Population statistics can help algorithms find brain structures in new scans and detect abnormalities (Thompson et al., 1997, 2001; Csernansky et al., 1998; Ashburner and Friston, 2000; Narr et al., 2001; Fischl and Dale, 2001). They can also identify systematic patterns of anatomy and function (e.g. Giedd et al., 1999; Sowell et al., 1999, 2001; Paus et al., 1999; Good et al., 2001), and uncover surprising relationships between genotype and phenotype (Styner and Gerig, 2001; Thompson et al., 2001; Cannon et al., 2001).

Increased Automation. Brain mapping analyses often draw upon hundreds or even thousands of images (Evans et al., 1994; Good et al., 2001). Computational approaches must therefore distil information from these images in a highly automated way. This challenge has driven developments in automated image registration and warping methods (Woods

et al., 1998; Toga, 1998; Ashburner et al., 1999; Guimond et al., 1999; Thompson et al., 2000; Shattuck and Leahy, 2001), as well as techniques for rapid image segmentation and labeling (Collins et al., 1995). As brain databases grow at a near-exponential pace, very large image analyses can now be run through client-server software pipelines. These intensive analyses may be performed on a remote server, aided by supercomputing resources to mine data for patterns and population trends (Toga et al., 2001; cf. Zijdenbos et al., 1996; Warfield et al., 1998; Megalooikonomou et al., 2000).

In this chapter, we review recent advances in image analysis that have enabled the creation of **population-based brain atlases** (Mazziotta et al., 1995, 2001; Thompson et al., 2000). These atlases combine imaging data from healthy and diseased populations, and have a range of exciting applications in neuroscience. They describe how the brain varies with age, gender, demographics. They also provide a comprehensive approach for studying a particular population subgroup, with a specific disease or neuropsychiatric disorder, for instance.

What do Population-Based Atlases Contain? Traditional single-subject atlases represent anatomy in a 3D coordinate system. Population-based atlases do so as well, but they contain anatomical models from many individuals. They store population averages, templates, and statistical maps, to summarize features of the population.

Central to the concept of all atlases is the idea of a common 3D reference space. The anatomy of the atlas, and new datasets that are aligned to it, can then be referred to using 3D spatial coordinates. Image registration techniques are typically used to align new datasets with the anatomic atlas (see Toga and Thompson, 2001 for a review). Multiple datasets can then be compared in a common coordinate space. Multi-modality atlases (Fig. 1) bring together and correlate brain maps from diverse imaging devices. Changes in anatomical morphology can then be related to differences in underlying neurochemistry and molecular content (Poxton et al., 1998; Mega et al., 1999). Atlases may also contain derived computational maps of various types. For instance they may contain normative statistics on anatomic variability, or on rates of brain change in development or disease. Dynamic maps of growth patterns in development are of particular interest (Lange et al., 1997; Giedd et al., 1999; Sowell et al., 1999; Thompson et al., 2001).

Relating all these structural and dynamic maps to genetic, therapeutic, and cognitive factors presents specific mathematical challenges. Among the armory of mathematical tools in building an atlas are cortical flattening approaches (Section 4), warping algorithms (Section 8), modeling approaches from population genetics (Section 9), and new results in random field theory. These mathematical tools give a multi-subject atlas its power to reveal generic patterns of brain structure and function not observable in an individual (Thompson et al., 2000).

Disease-specific brain atlases are a particular type of population atlas. They provide a unique perspective on the anatomy and physiology of a particular disease (Mega et al., 1999; Thompson et al., 2000a,b,c, 2001; Narr et al., 2001a,b; Cannon et al., 2001). These atlases store multi-modality imaging data from a specific clinical subpopulation, such as patients with Alzheimer's disease (Mega et al., 1997, 1999), schizophrenia (Narr et al., 2001; Thompson et al., 2001), or a psychiatric disorder such as fetal alcohol syndrome (Sowell et al., 2001). The populations may be stratified to reflect a particular clinical subgroup, including those at familial risk for a disease (Cannon et al., 2001), those receiving different medications (Thompson et al., 2001), or those with a specific symptom profile or genotype.

Genetic Atlases. Inclusion of genetic data in these atlases makes it possible to go beyond describing a disease to investigate its causes. Novel mathematics can be used to mine imaging data, and to identify genetic sources of variation. This allows the direct mapping of genetic influences on brain structure, and lets us quantify heritability for different features of the brain (Thompson et al., 2001; see Section 9). Familial, twin and genetic linkage studies have recently begun to expand the atlas concept to tie together genetic and imaging studies of disease. Atlases that contain genetic brain maps, and a means to analyze them, can help screen relatives for inherited disease (Cannon et al., 2001). They also offer a framework to mine large imaging databases for risk genes and quantitative trait loci (Gottesman, 1997), as well as genetic and environmental triggers of disease.

2. Atlases in Brain Mapping

Brain Maps and Atlases. Since the development of computerized tomography (CT; Hounsfield, 1973) and magnetic resonance imaging techniques (Lauterbur, 1973), maps of brain structure have typically been based upon 3D tomographic images (Damasio, 1995). Angiographic or spiral CT techniques can also visualize vascular anatomy (Fishman, 1997), while diffusion tensor images can even reveal fiber topography *in vivo* (Turner et al., 1991; Jacobs and Fraser, 1994; Mori et al., 2001). These brain maps can be supplemented with high-resolution information from anatomic specimens (Talairach and Tournoux, 1988; Ono *et al.*, 1990; Duvernoy, 1991) and a variety of histologic preparations which reveal regional cytoarchitecture (Brodmann, 1909) and regional molecular content such as myelination patterns (Smith, 1907; Mai *et al.*, 1997), receptor binding sites (Geyer *et al.*, 1997), protein densities and mRNA distributions. Other brain maps have concentrated on function, quantified by positron emission tomography (PET; Minoshima *et al.*, 1994), functional MRI (Le Bihan, 1996), electrophysiology (Avoli *et al.*, 1991; Palovcik *et al.*, 1992) or optical imaging (Cannestra et al., 1996). Additional maps have been developed to represent neuronal connectivity and circuitry (Van Essen and Maunsell, 1983), based on compilations of empirical evidence (Brodmann, 1909; Berger, 1929).

Each of these brain mapping approaches produces data with a different scale and resolution, and none is inherently comparable with any other. Their correlative potential is therefore underexploited unless algorithms are applied to align them into a common reference space. This common coordinate system can be provided by a **brain atlas**.

Aligning Multiple Subjects' Data to an Atlas. To address difficulties in comparing brain maps, brain atlases (e.g. Talairach and Tournoux, 1988; Swanson, 1992; Evans et al., 1994; Mazziotta et al., 1995; Spitzer et al., 1996; Kikinis et al., 1996; Drury and Van Essen, 1997; Schmahmann et al., 1999) provide a structural framework in which individual brain maps can be integrated. Most brain atlases are based on a detailed representation of a single subject's anatomy in a standardized 3D coordinate system, or stereotaxic space. The chosen data set acts as a template on which other brain maps (such as functional images) can be overlaid. The anatomic data provides the additional detail necessary to accurately localize activation sites, as well as providing other structural perspectives such as chemoarchitecture. Digital mapping of structural and functional image data into a common 3D coordinate space is a prerequisite for many types of brain imaging research, as it supplies a quantitative spatial reference system in which brain data from multiple subjects and modalities can be compared and correlated.

Talairach Reference System. The first brain atlas used widely by the brain mapping community was that defined by the neurosurgeon Jean Talairach (Talairach and Tournoux, 1988). Using a stereotaxic device anchored to a patient's skull, neurosurgeons can accurately position surgical apparatus within a patient's brain to target biopsy locations, epileptic foci, and vascular lesions identified in 3D reference coordinates. The Talairach atlas was developed before intraoperative imaging, to make it easier to identify deep nuclei in stereotaxic coordinates. At the time, these structures were imaged with very limited resolution using pneumoencephalography.

Alignment to an Atlas. In addition to a series of labeled anatomical plates, reconstructed from histologic material, Talairach defined a mechanism to transfer new images onto the atlas. In the Talairach stereotaxic system, piecewise affine transformations are applied to 12 rectangular regions of brain, defined by vectors from the anterior and posterior commissures to the extrema of the cortex. These transformations re-position the anterior commissure of the subject's scan at the origin of the 3D coordinate space, vertically align the interhemispheric plane, and horizontally orient the line connecting the two commissures. Each point in the incoming brain image, after it is 'warped' into the atlas space, is labeled by an (x,y,z) address referable to the atlas brain. Although originally developed for surgical purposes, the Talairach stereotaxic system rapidly became an international standard for reporting functional activation sites in PET studies, allowing researchers to compare and contrast results from different laboratories (Fox et al., 1985, 1988; Friston et al., 1989, 1991). A recent tool for meta-analysis of functional imaging data, the *Talairach Daemon*, contains a digital version of the Talairach atlas. Using the atlas as a reference coordinate system, it provides spatially-indexed links to Brodmann areas, probabilistic maps of activation foci, and related scientific literature (Lancaster et al., 2000).

MRI Atlas Templates. The Talairach templates were based on *post mortem* sections of the brain of a 60 year-old female subject, which clearly did not reflect the *in vivo* anatomy of subjects in activation studies. The atlas plates were also compromised by having a variable slice separation (3 to 4 mm), and inconsistent data from orthogonal planes. To address these limitations, a composite T1-weighted MRI dataset was constructed from 305 young normal subjects (239 males, 66 females; age: 23.4 ± 4.1 years) whose scans were individually mapped into the Talairach system by a 9-parameter linear transformation, intensity normalized, and averaged on a voxel-by-voxel basis (Evans et al., 1994). The resulting average brain made it easier to develop automated image alignment methods to map new MRI and PET data into a common space. The *International Consortium for Brain Mapping* (ICBM; Mazziotta et al., 1995; 2001) subsequently applied the same image averaging procedure to a subset of 152 brains. This produced a template that is widely used as part of the *Statistical Parametric Mapping* image analysis package (SPM99b; Friston et al., 1995).

Aligning New Data to an Atlas. New MR data are typically aligned with an atlas template by defining a measure of intensity similarity between the overlapping dataset and atlas. This measure of fit is optimized by tuning the parameters of the alignment transformation until the similarity is maximized (Woods et al., 1998; Ashburner, 2001). Intensity-based registration measures include 3D cross-correlation (Collins et al., 1994,1995), ratio image uniformity (Woods et al., 1992, 1993), or mutual information (Viola et al., 1995; Wells et al., 1997), or the summed squared differences in intensity between the scans (Christensen et al., 1993, 1996; Ashburner et al., 1998; Woods et al., 1998). Both linear (global) transforms, and nonlinear transforms may be used, and these registration methods are reviewed in detail elsewhere (Toga, 1998; Thompson et al., 2001). Any alignment transformation defined for one modality, such as MRI, can be identically applied to another modality, such as PET, if a previous cross-modality intrasubject registration has been performed (Woods et al., 1993). For the first time then, PET data could be mapped into stereotaxic space via a correlated MR dataset (Woods et al., 1993; Evans et al., 1994). Registration algorithms therefore made it feasible to automatically map data from a variety of modalities into an atlas coordinate space based directly on the Talairach reference system.

Other Standardized Brain Templates. Individual brains differ substantially in structure. If MRI scans are averaged after only a linear alignment into stereotaxic space, the resulting dataset is blurred in the more variable anatomic regions (Evans et al., 1994). Many structures are washed away rather than reinforced. This problem can be circumvented using nonlinear registration to define a mean anatomic template for a population, with well-resolved cortical features (see Section 5; Collins et al., 1994; Thompson et al., 2000). Alternatively, an atlas may be based on a single individual, as in the Karolinska Brain Atlas project (Greitz et al., 1991; Roland and Zilles, 1996), the *Digital Anatomist* project in Seattle (Sundsten et al., 1991; Brinkley et al., 1997). Other atlasing projects have preferred multimodality data from a single subject, including the Harvard Brain Atlas (Kikinis et al., 1996), the *VOXEL-Man* atlas (Höhne et al., 1992; ; Tiede et al., 1993; Pommert et al., 1996), and the *Visible Human Project* (Spitzer, 1996).

High-Resolution Atlas Templates. A recent innovation in the collection of atlas quality MRI uses multiple scans (N=27) and a registered average of a single individual to overcome the lack of contrast and relatively poor signal to noise of tomographic data (Holmes et al., 1998; Kochunov et al., 2001). This high-resolution brain template is used in the *BrainWeb* simulator (Collins et al., 1998), the SPM functional imaging package (Friston et al., 1995), and serves as a template in a recent cerebellar atlas (Schmahmann et al., 1999). Unlike with a population-based atlas, some bias is implicit in selecting an individual brain as an atlas target. These biases may be minimized by (1) selecting a brain that deviates minimally from a population (Lancaster et al., 2000), or by (2) explicitly transforming an individual brain, using image warping methods, to reflect the mean geometry of a group (Kochunov et al., 2001).

Interoperability. A vexing issue with the proliferation of atlas templates is the need to relate imaging data that has been aligned to different atlases, sometimes with different registration methods (Haller and Vannier, 1998). Efforts to mutually register the atlases themselves (Letovsky et al., 1998) have resulted in the fusion of the Talairach atlas with the Ono sulcal atlas (Ono et al., 1990). The Talairach templates have recently been fused (Nowinski et al., 2000) with the Schaltenbrand and Wahren brain atlas (1977), which represents deep nuclear anatomy, and is often consulted in preoperative planning of thalamic surgery (Niemann and van Nieuwenhofen, 1999). Because of differences in brain shape, the ICBM average brain templates are slightly larger (in particular higher, deeper and longer) than the original

Talairach brain. Formulas have been estimated to reconcile data expressed in each system (Brett et al., 2001; Rorden and Brett, 2001). These formulas refer activation foci in ICBM space to Brodmann areas labeled on the Talairach atlas.

Population Maps of Cytoarchitecture. Because Brodmann areas defined on the Talairach atlas are only approximate, probabilistic maps of cytoarchitecture are currently being compiled in standardized atlas spaces, such as that defined by the ICBM templates (Geyer et al., 2001; Rademacher et al., 2001; Grefkes et al., 2001; Amunts and Zilles, 2001). Brodmann areas may also be defined on unfolded cortical templates (Carman et al., 1995; Hurdal et al., 1999; Van Essen et al., 2001; Zeineh et al., 2001; Fischl and Dale, 2001; Thompson et al., 2001; see Section 4). These templates can, in some cases, be projected back into individual datasets in atlas space to help localize activation foci (Drury and Van Essen, 1997; Rorden and Brett, 2001). Finally, research is underway to transfer brain mapping data between anatomic templates with nonlinear warping approaches (Fig. 2; Toga, 1998). For different applications, different templates may have different merits and biases (Thompson et al., 2001; Kochunov et al., 2001a,b). A reasonable goal is therefore to develop mathematics to compute consistent (e.g. symmetric and transitive) mappings between the atlas templates that are most widely used (Christensen et al., 1999).

3. Anatomical Modeling

The development of group anatomic atlases is motivated by understanding anatomical variations in human populations. Even after aligning brain data into a common reference space, such as that defined by an atlas, individual anatomy still varies widely. These variations are so great, that disease-specific differences are hard to identify. Computational techniques have therefore been designed to encode these statistical variations, which are greatest at the cortex. Population atlases can then identify systematic effects on brain structure, such as differences due to age, gender, disease processes, therapy, or genetic risk.

Computational Anatomy. Efforts to uncover new patterns of altered structure and function in individuals and clinical populations have led to the new field of *computational anatomy* (Grenander and Miller, 1998; Thompson et al., 2001; Fischl et al., 1999; Davatzikos et al., 1996; Guimond et al., 2001; Worsley et al., 2000; Ashburner, 2001; see Thompson and Toga, 2001, for a review). This growing field has powerful applications in neuroscience, revealing, for example, how the brain grows in childhood (Thompson et al., 2000), how genes affect brain structure (Thompson et al., 2001; Cannon et al., 2001; Styner and Gerig, 2001), and how diseases such as Alzheimer's, schizophrenia, or multiple sclerosis evolve over time or respond to therapy (Zijdenbos et al., 1996; Subsol et al., 1997; Freeborough and Fox, 1998; Thompson et al., 2001; Haney et al., 2001). Fundamental to the goals of computational anatomy is the ability to create *average* maps of brain structure. Average templates are under rapid development for the *Macaque* brain (Grenander and Miller, 1998), and for individual structures such as the *corpus callosum* (Davatzikos, 1996; Gee et al., 1998), central sulcus (Manceaux-Demiau et al., 1998), cingulate and paracingulate sulci (Paus et al., 1996; Thompson et al., 1997), hippocampus (Haller et al., 1997; Joshi et al., 1998; Csernansky et al., 1998; Thompson et al., 1999) and for transformed representations of the human and *Macaque* cortex (Van Essen et al., 1997; Grenander and Miller, 1998; Thompson et al., 1999; Fischl and Dale, 2001).

One approach to create average anatomical maps is based on the concept of *parametric mesh* modeling. Anatomical models based on parametric meshes can be valuable components of population atlases; they can identify and localize systematic anatomic differences in patients with diseases such as Alzheimer's, schizophrenia, and developmental disorders. We review their construction and uses next.

Parametric Meshes. The modeling of structures in the brain using parametric curves and surfaces (Fig. 3) offers exciting advantages for detecting generic patterns in anatomy (Thompson et al., 1996a,b, 1998; Joshi et al., 1998; Vaillant et al., 1998; MacDonald et al., 2000; Fischl et al., 2001; Styner and Gerig, 2001; Gerig et al., 2001). The idea is to overlay a computational grid on the boundary of an anatomical structure, such as the ventricles (Fig. 4) or the cortex (see Section 4). The surface grid structure helps in building average templates of anatomy and statistics that capture its variation (Fig. 3). In simple cases, surface models may represent a single structure such as the *corpus callosum* (Thompson et al., 1998; Fig. 5), deep sulcal surfaces (Thompson et al., 1996a,b, 1997, 1998; Le Goualher et al., 2000),

deep motor nuclei (Blanton et al., 2000), or the hippocampus and amygdala (Narr et al., 2001; Thompson et al., 2001). The resulting computational models can represent anatomical structures in geometric detail, including 3D surface boundaries (e.g. basal ganglia, cortex), as well as 2D and 3D curves (*e.g.* the corpus callosum at midline, sulcal fundi lying in the cortex). As well as serving as key building blocks for brain atlases, surface models can also drive algorithms for nonlinear warping (Thompson and Toga, 1996; Davatzikos et al, 1996), and can assist in computing growth patterns and other dynamic changes in anatomy (Thompson et al., 2000; Section 8).

Parametric mesh modeling approaches define a mapping of a regular 2D grid onto a complex 3D surface (Fig. 3). The concept is similar to stretching a regular net over an object. The explicit geometry provided by this approach makes it easy to derive shape descriptors such as surface curvature, extent, area, fractal dimension and geometric complexity (Thompson *et al.*, 1996; see Blanton et al., 2001; Narr et al., 2000 for applications). These morphometric statistics may be altered in disease, even if structure volumes are not statistically different. Narr et al. (2000) observed that callosal area did not discriminate schizophrenic groups from healthy controls, while shape measures provided a distinct group separation. Wang et al. (2001) found that hippocampal shape descriptors had greater power to distinguish patients from controls than volumetry, while others have argued that each approach provides complementary information (Gerig et al.. 2001; Thompson et al., 2001).

Advantages of Surface Models. Surface modeling also provides advantages for data visualization. The surface format may be triangulated and rendered graphically, or even animated (Toga, 2001). Texture maps, statistics, and dynamic patterns of functional activations may also be superimposed on graphical renderings of anatomy (e.g., Höhne et al., 1996; Kikinis et al., 1996; Thompson et al., 1997; Zeineh et al., 2001). Imposition of an identical regular structure on surfaces from different subjects makes them easy to compare and average together. Points on each surface with the same mesh coordinate occupy similar positions in relation to the geometry of the surface they belong to, and are therefore regarded as homologous. More complex methods can enforce additional correspondences when averaging surfaces, such as sulcal curves lying in the cortex; these issues are covered in Section 4.

Generating Surfaces. Some surface models are easy to extract automatically. Examples include the cortex, cerebellar surface, corpus callosum, and hippocampus (Haller et al., 1997; Joshi et al., 1998; MacDonald et al., 2000; Shattuck and Leahy, 2001; Fischl and Dale, 2001; Pitiot et al., 2002). Structures that are more difficult to extract automatically can be traced manually in serial sections, or in 3D, using a formal anatomical protocol with quantified reliability (e.g. Sowell *et al.*, 2001; Zhou et al., 2001). Manual traces are subsequently converted to uniform mesh format using a re-gridding algorithm, which makes the sampled points spatially uniform (Thompson et al., 1996a,b). Typically in building a brain atlas, a mixture of manual and automated methods is used, to ensure greatest accuracy. For example, the cortex may be extracted automatically, but gyral landmarks may be traced on it manually using a protocol with known, quantified reliability.

Anatomical Averaging. An average anatomical surface is generated for a group of subjects by averaging the vector locations of corresponding surface points across the subject group. This process is repeated for each point on the surface. Suppose we have a family, ö, of *N* different surface meshes representing a particular structure in *N* separate individuals, drawn from a specific population. If $\mathbf{r}_i(u,v)$ is the 3D position in stereotaxic space of the point with parametric coordinates (u,v) on the *i*th mesh, then the average sulcal surface is given by another mesh of the form:

$$\mathbf{r}_{\text{:}}(u,v) = (1/N)\mathbf{G}_{i=1 \text{ to } n}\, \mathbf{r}_i(u,v), \quad \text{œ}(u,v). \qquad (1)$$

Information on anatomic variability can also be retained, and shown as a *variability map* (Thompson et al., 1996, 1998). To map variability, individual deviations from the average surface are measured by computing 3D displacement maps (Fig. 3). These are patterns of 3D displacement vectors that would be required to re-shape the average surface into the shape of a specific individual. If surface locations $\mathbf{r}_i(u,v)$ in subject *i*, are indexed by parametric coordinates (u,v), then deviations of these locations in individual *i* from the mean anatomical surface are given by the set of displacement vectors:

$$\mathbf{d}_i(u,v) = \mathbf{r}_i(u,v) - \mathbf{r}_{\bar{}}(u,v), \quad (2)$$

for all pairs of corresponding grid points $\mathbf{r}_i(u,v)$ and $\mathbf{r}_{\bar{}}(u,v)$. For each (u,v), the associated displacement maps $\mathbf{d}_i(u,v)$ represent a sample of (vector) observations from a zero-mean, spatially anisotropic probability distribution (Thompson et al., 1996). The variability of the surface points can be encoded using the covariance matrix, or tensor, of the deformation maps:

$$\mathbf{Q}_{\ddot{o}}(u,v) = [1/(N-1)] \sum_{i=1 \text{ to } N} \mathbf{d}_i(u,v)\mathbf{d}_i(u,v)^T \quad (3).$$

This matrix stores the shape, or preferred directions, of anatomic variability in the brain (Thompson et al., 1996; Cao and Worsley, 1999; Section 6). Perhaps the simplest measure of anatomic variability is the root mean square magnitude of the 3D displacement vectors, assigned to each point, in the surface maps from individual to average. This variability pattern can be visualized as a color-coded map. This map helps pick out regions that are highly variable across subjects, such as the occipital horns of the ventricles (Fig. 4), and the gyral patterns of the perisylvian cortices.

Emerging Features. An example application is the analysis of ventricular anatomy in Alzheimer's disease. Two features are observed in the average anatomical maps (Fig. 4) that may not be apparent, or would be difficult to localize, with conventional volumetry. First, the ventricles are larger in Alzheimer's disease than in healthy controls; second, there is a marked ventricular asymmetry (left larger than right), which is most pronounced in the occipital horns. Finally there is considerable anatomic variation (*red colors*) in occipital horn regions, which obscures these average patterns in individual datasets. Once identified, these features can be assessed statistically in new datasets, or an individual anatomy can be compared with the average maps in the atlas. Conventional morphometric statistics may also be used to describe these differences, such as lengths and curvatures, which are typically easiest to understand. Alternatively the shapes can be compared directly, using mathematics to encode the population variability in anatomical shape (see *Footnote 1*).

Footnote 1. *How Can Anatomical Shapes be Compared?* So far (e.g. in Fig. 3) we have considered variations of surface points individually (Thompson et al., 1999; Fig. 3,4). The notion of overall (global) shape similarity and variability can also be encoded using a *point distribution model* or *active shape model* (ASM; Cootes et al., 1995; Davies et al., 2001; Frangi et al., 2001; Poxton et al., 1998). These statistical models are popular in the computer vision community for face recognition (Sclaroff and Pentland, 1994) and statistically-guided image segmentation (Duta and Sonka, 1997). They use principal component analysis to describe shape variation in a population using a small number of parameters. By capturing the notion of allowable anatomical shapes, they make it easier to find structures in new images, and implicitly quantify the abnormality in an anatomic structure. An anatomical shape is considered as a single vector of coordinates. The statistical distribution of different shapes estimated from a training set, or a refernce atlas, of examples. For N shapes described as vectors of k different 3D landmark points $\mathbf{s}_i = (x_{i1}, x_{i2}, x_{i3}, \ldots, x_{ik1}, x_{ik2}, x_{ik3})$, the individual anatomies form a distribution in a $3k$-dimensional space, which is approximated by a linear model of the form:

$$\mathbf{s} = \mathbf{s}_{\blacksquare} + \mathbf{F}\,\mathbf{b} \quad (4).$$

Here $\mathbf{s}_{\blacksquare} = [1/N]\ (\Sigma_{i=1 \text{ to } N}\ \mathbf{s}_i)$ is the mean shape vector, $\mathbf{b}$ is the shape parameter vector of the anatomical model, and $\mathbf{F}$ is a matrix whose columns are the principal components (unit eigenvectors) of the covariance matrix:

$$\mathbf{S} = [1/(N-1)]\ (\sum_{i=1 \text{ to } N}\ (\mathbf{s}_i - \mathbf{s}_{\blacksquare})(\mathbf{s}_i - \mathbf{s}_{\blacksquare})^T) \quad (5).$$

The shape information in the population is then compacted in a new matrix $\mathbf{F}^*$ whose columns are the first t eigenvectors of $\mathbf{F}$, corresponding to the largest eigenvalues, $\lambda_1 \geq \ldots \geq \lambda_t$. These are the *principal modes* of shape variation. They describe the most significant types of variation, in terms of the proportion of variance explained. Individually they describe how boundary points tend to move together as the shape varies. Then we can approximate any anatomical shape by adding a linear combination of the eigenvectors to the mean vector, or center point, which describes the average shape: $\mathbf{s}^* = \mathbf{s}_{\blacksquare} + \mathbf{F}^*\mathbf{b}^*$. Here $\mathbf{b}^* = (b_1 \ldots b_t)$ is a t-dimensional vector of weights, or shape parameters, which can be computed for a given shape, from the formula:

$$\mathbf{b}_i^* = \mathbf{F}^{*T}(\mathbf{s}_i - \mathbf{s}_{\blacksquare}) \quad (6).$$

If Gaussian distributions are assumed, the abnormality of an anatomical shape can be measured by its Mahalanobis distance from the mean (cf. Thompson et al., 1996:

$$D^2_t = \Sigma_{i=1 \text{ to } t} \, b_i^{\,2} / \lambda_i^{\,2} \qquad (7).$$

For large *N*, this measure follows a chi-squared distribution with *t* degrees of freedom, and is proportional to the logarithm of the probability of obtaining the shape from the measured distribution of shapes. Multivariate analysis can then assess effects of diagnosis, gender, or other covariates, on the shape vector $\mathbf{b}_i^*$ (Joshi et al., 1998; Gerig et al., 2001).

Anatomical Shape Classification. The above approach represents anatomical shapes in terms of the eigenvectors of statistical variation, learned from a sample or training set. Wang and Staib (2000) apply this shape encoding in a Bayesian framework to locate the corpus callosum and basal ganglia in new images, based on a training set. A more complex variant of this approach is Grenander's shape modeling approach (Grenander and Miller, 1998). This models anatomical shapes in terms of a basis of mathematical functions, such as spherical harmonics (Thompson and Toga, 1996; Csernansky et al., 1998; Gerig et al., 2001), Oboukhov expansions (Joshi et al., 1998; Gerig et al., 2001), or elliptical Fourier series (Staib and Duncan, 1992). These functions are in fact eigenfunctions of self-adjoint differential operators (such as the Laplacian and Cauchy-Navier operator), and they can be thought of as the modes of vibration of physical systems described by partial differential equations (Grenander and Miller, 1998; Thompson et al., 2001). Sclaroff and Pentland (1994) also represent shape differences in terms of the physical modes of vibration of the original shape. Both of these statistical and physical approaches are designed to create efficient representations of complex shapes in terms of a small number of numerical parameters. The resulting parameter set can then be subjected to multivariate analysis or linear discriminant analysis to classify and characterize anatomical shape abnormalities in disease (Joshi et al., 1998). Golland et al. (2001) extended this approach to classify 3D models of the hippocampus/amygdala complex in schizophrenia relative to healthy controls. Rather than use surfaces directly, they used a 3D distance map as a shape descriptor, whose value at any point is the nearest distance to the surface. A classifier was developed based on support vector machines (SVMs), a popular classification technique in machine learning theory. A measure based on the Vapnik-Chervonenkis dimension (Vapnik, 1995) was employed to estimate the smallest samples size necessary for statistical significance, an important feature in atlas construction (Golland et al., 2000).

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In building average brain models in an atlas, parametric mesh averaging works well for simple structures, but needs some modifications when creating average templates of the cortex. This procedure is described next.

4. Population Maps of the Cortex

Understanding cortical anatomy and function is a major focus in brain research. Many diseases affect the anatomy and organization of the cortex. The cortex also changes over time, as in aging, Alzheimer's disease (Mega et al., 2000), or developmental disorders (Sowell et al., 1999; Thompson et al., 1998, 2001; Blanton et al., 2001). The gyral patterns of the human cortex provide a fairly reliable guide to its functional organization, although the congruence is not absolute (Brodmann, 1909; Rademacher et al., 1993; Amunts and Zilles, 2001). Since most imaging studies of brain function focus on the cortex, it is especially important to be able to pool cortical brain mapping data from subjects whose anatomy is different (Zeineh et al., 2001). Despite interest in analyzing patterns of cortical variation for interesting effects, general patterns of organization are hard to discern, as are systematic alterations in disease. Sulcal pattern variation (Fig. 6; Steinmetz et al., 1990; Ono et al., 1990; Thompson et al., 1996; Le Goualher et al., 1999, 2000; MacDonald et al., 2000) also complicates attempts to define statistical criteria for abnormal cortical anatomy.

In the following section we outline a framework for analyzing cortical anatomy. Specialized algorithms compare and average cortical anatomy across subjects and groups, map its variation and asymmetry, and chart patterns of abnormality or brain change. Rapid developments are being made in the mathematics of cortical mapping (Angenent et al., 1999; Hurdal et al., 1999; Joshi et al., 1995; Haker et al., 2000; Bertalmio et al., 2000; Fischl et al., 2001). Signal detection methods based on random field theory, used widely in brain mapping, are also being optimized to handle cortical surface data (Thompson *et al.*, 1997, 2001; Cao and Worsley, 1999; Chung et al., 2001; Taylor and Adler, 2001). These approaches draw upon parametric surface methods, but supplement them with additional warping, gyral pattern

matching, and diffusion smoothing approaches that make comparison of cortical data tractable.

Cortical Modeling. A major challenge in investigations of disease is to determine (1) whether cortical organization is altered, and if so, which cortical systems are implicated, and (2) whether normal features of cortical organization are lost, such as sulcal pattern asymmetries (Kikinis et al., 1994; Bilder et al., 2000; Narr et al., 2001; Sowell et al., 2001). These questions motivate methods to create a disease-specific average models of the cortex, and a statistical framework to compare individual and group average models with normative data.

Cortical Parameterization. Several methods exist to generate surface models of the cortex from 3D MRI scans. Some of these impose a tiled, parametric grid structure on the anatomy, which is used as a coordinate framework to support subsequent computations. In '*bottom-up'* approaches (e.g. Fischl *et al.*, 1999; Haker *et al.*, 1999; Shattuck and Leahy, 2001), a voxel-based segmentation of white matter is generated first, using a tissue classifier or level set methods (Sapiro, 2000). Its topology is then corrected using graph theoretic methods (Shattuck and Leahy, 2001; Xiao Han et al., 2001). This creates a single, closed, simply connected surface homeomorphic to a sphere (Fischl et al., 1999; Hurdal et al., 1999; Rettman et al., 2000; Shattuck and Leahy, 2001). The surface is tiled using triangulation methods such the *Marching Cubes* algorithm (Lorensen and Kline, 1987). The gridded surface is then inflated, using iterative smoothing, to a spherical shape. By inverting this inflation mapping, this allows a spherical coordinate system to be projected back onto the 3D model, for subsequent computations. Alternatively the 3D surface may be flattened to a 2D plane (Fig. 7; Drury and Van Essen *et al.*, 1997; Van Essen et al., 1997; Thompson *et al.*, 1997; Angenent *et al.*, 1999; Hurdal *et al.*, 1999), inducing an alternative 2D parameterization onto the original 3D surface.

A second ('*top-down'*) type of surface extraction method (Davatzikos, 1996; MacDonald, 1998; Kabani et al., 2000) begins with a spherical or ellipsoidal surface that is already tiled. This parametric surface is successively moved, under image-dependent forces, reshaping it into the complex geometry of the cortical boundary (see Xu *et al.*, 1999, for work on *gradient vector flow*). This avoids the need for topology correction, as a single, fixed, grid structure is established at the start, and mapped with a continuous deformation onto each anatomy. Complex constraints are, however, required while deforming the surface. These ensure that the surface does not self-intersect and adapts fully to the target geometry. The first (bottom-up) strategy turns the cortex into a sphere, while this latter approach deforms a sphere onto the cortex. Both approaches allow project a coordinate-system onto the anatomy, so that cortical locations can be referred to in surface-based coordinates.

Mapping Gyral Pattern Differences in a Population. Once cortical models are available for a large number of subjects, in a common 3D coordinate space, patterns of cortical variability can be calculated. The major gyri and sulci of the cortical surface have a similar spatial layout across subjects (Ono et al., 1990; Regis, 1994), even though their geometry varies substantially. In one approach (Thompson et al., 2000), a maximal set, or template, is specified, containing all primary sulci that consistently occur in normal subjects (*see Footnote 2*; Fig. 6(b),(c) shows some of these). This set of sulcal curves can be reliably identified manually by trained raters, so long as a formalized protocol and detailed anatomical criteria are followed (Sowell et al., 2001). Automated labeling of sulci is also the focus of intense study (Mangin et al., 1994; Vaillant and Davatzikos, 1997; MacDonald, 1998; Lohmann et al., 1999; Royackkers et al., 1999; Le Goualher et al., 1999; Zhou et al., 1999; Rettman et al., 2000; Tao et al., 2001; Caunce and Taylor, 2001).

Footnote 2. Several complications arise in identifying corresponding sulci across subjects. These can only be partially resolved using information on which sulci border known architectonic fields (Brodmann, 1909; Rademacher et al., 1993). Approximately a quarter of normal brain hemispheres have two cingulate gyri (the 'double parallel' conformation; Ono et al., 1990; Regis, 1994; Paus et al., 1999), and some individuals have two Heschl's gyri (Leonard et al., 1996), while others have only one. When there are two cingulate sulci, the outer (paracingulate) sulcus arguably matches the single sulcus in an individual with only one, as it bounds the Brodmann areas belonging to the limbic system. Interrupted sulci, in which a sulcal curve is broken into several segments, may also need to be connected and modeled as a single curve to facilitate matching (cf. Thompson et al., 1999; Sebastian et al., 2000). In rare cases, some pairs of sulci, such as the postcentral sulcus and the marginal ramus of the cingulate, meet the superior margin of the interhemispheric fissure in a different anterior-to-posterior order. Modeling of the graph-theoretic structure and connectivity of the sulci may also be necessary for a fuller understanding of cortical variation (Mangin et al., 1994).

Matching Cortical Patterns. Cortical anatomy can be compared, between any pair of subjects, by computing the warped mapping that elastically transforms one cortex into the shape of the other. Due to variations in gyral patterning, cortical differences among subjects will be severely underestimated unless elements of the gyral pattern are matched from one subject to another. This matching is also required for cortical averaging; otherwise, corresponding gyral features will not be averaged together. Transformations can therefore be developed that match large networks of gyral and sulcal features with their counterparts in the target brain (Thompson and Toga, 1996, 1997; Davatzikos, 1996; Van Essen et al., 1997; Fischl et al., 1999). In a recent anatomically-based approach, we match 38 elements of the gyral pattern, including the major features that are consistent in their incidence and topology across subjects (see Thompson et al., 2001 for details; Sowell et al., 2000; cf. Ono et al., 1990; Leonard et al., 1996; Kennedy et al., 1998).

To find good matches among cortical regions we perform the matching process in the cortical surface's parametric space, which permits more tractable mathematics (Fig. 7). This vector flow field in the parametric space indirectly specifies a correspondence field in 3D, which drives one cortical surface into the shape of another. This mapping not only matches overall cortical geometry, but matches the entire network of the 38 landmark curves with their counterparts in the target brain, and thus is a valid encoding of cortical variation. Details of this procedure are given in *Footnote 3*.

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Footnote 3. *Mathematics of Spherical, Planar Maps of Cortex.* We recently applied this matching approach to measure anatomic variability in a database of 96 cortical models (extracted from an MRI database with the algorithm of MacDonald, 1998; Thompson et al., 2001). Since cortical models were created by driving a tiled, spherical mesh into the configuration of each subject's cortex, any point on the cortical surface maps to exactly one point on the sphere and *vice versa*. Each cortical surface is parameterized with an invertible mapping D_p,D_q: $(r,s)\rightarrow(x,y,z)$, so sulcal curves and landmarks in the folded brain surface can be reidentified in a spherical map (*cf.* Fischl et al., 1999). To retain relevant 3D information, cortical surface point position vectors (x,y,z) in 3D stereotaxic space were color-coded using a unique RGB color triplet, to form an image of the parameter space in color image format (Fig. 7(f)). These spherical locations, indexed by two parameters, can also be mapped to a plane (Fig. 7(e); Thompson et al., 1997). Cortical differences between any pair of subjects were calculated as follows. A flow field was first calculated that elastically warps one flat map onto another from the other subject (Fig. 7; or equivalently, one spherical map onto the other). On the sphere, the parameter shift function $\mathbf{u}(\mathbf{r}):\Omega \rightarrow \Omega$, is given by the solution $F_{pq}:\mathbf{r}\rightarrow\mathbf{r}-\mathbf{u}(\mathbf{r})$ to a curve-driven warp in the spherical parametric space $\Omega=[0,2\pi)\times[0,\pi)$ of the cortex (Fig. 7; Thompson et al., 1997). For points $\mathbf{r}=(r,s)$ in the parameter space, a system of simultaneous partial differential equations can be written for the flow field $\mathbf{u}(\mathbf{r})$:

$$L^{\ddagger}(\mathbf{u}(\mathbf{r})) + \mathbf{F}(\mathbf{r}-\mathbf{u}(\mathbf{r})) = \mathbf{0},\ \forall \mathbf{r}\in\Omega,\ \text{with}\ \mathbf{u}(\mathbf{r}) = \mathbf{u_0}(\mathbf{r}),\ \forall \mathbf{r}\in M_0\cup M_1. \qquad (8)$$

Here M_0, M_1 are sets of points and (sulcal or gyral) curves where displacement vectors $\mathbf{u}(\mathbf{r})=\mathbf{u_0}(\mathbf{r})$ matching corresponding anatomy across subjects are known. The flow behavior is modeled using equations derived from continuum mechanics, and these equations are governed by the Cauchy-Navier differential operator

$$L = \mu\nabla^2+(\lambda+\mu)\nabla(\nabla^T\bullet) \qquad (9)$$

with body force $\mathbf{F}$ (Gee et al., 1998; Gramkow, 1998). The only difference is that $L^{\ddagger}$ is the *covariant* form of the differential operator L (for reasons explained in *footnote 2*). This approach not only guarantees precise matching of cortical landmarks across subjects, but creates mappings that are independent of the surface metrics, and therefore independent of how the surfaces are gridded (parameterized).

Warping One Cortex to Another. Since the cortex is not a *developable* surface, it cannot be given a parameterization whose metric tensor is uniform (Van Essen and Maunsell, 1983). As in fluid dynamics or general relativity applications, the intrinsic curvature of the solution domain can be taken into account when computing flow vector fields in the cortical parameter space, and mapping one mesh surface onto another. In the *covariant tensor* approach (Thompson et al., 2001), correction terms (Christoffel symbols, $\mathbf{G}^{\mathbf{i}}_{\mathbf{jk}}$) make the necessary adjustments for fluctuations in the metric tensor of the mapping procedure. In the partial differential equations (1), we replace L by the covariant differential operator $L^{\ddagger}$. In $L^{\ddagger}$, all L's partial derivatives are replaced with *covariant* derivatives (Burke, 1985). These covariant derivatives are defined with respect to the metric tensor of the surface domain where calculations are performed. The covariant derivative of a (contravariant) vector field, $u^i(\mathbf{x})$, is defined as

$$u^i{}_{,k} = \partial u^j/\partial x^k + \mathbf{G}^{\mathbf{j}}_{\mathbf{ik}}\, u^i \qquad (10)$$

where the *Christoffel symbols of the second kind* (Einstein, 1914), $\mathbf{G}^{\mathbf{j}}_{\mathbf{ik}}$, are computed from derivatives of the metric tensor components $g_{jk}(\mathbf{x})$:

$$\mathbf{G}^{\mathbf{i}}_{\mathbf{jk}} = (1/2)\, g^{il}\,(\partial g_{lj}/\partial x^k+\partial g_{lk}/\partial x^j-\partial g_{jk}/\partial x^l). \qquad (11)$$

These correction terms are then used in the parameter space flow that matches one cortex with another. Note that a parameterization-invariant variational formulation could also be used to minimize metric distortion when mapping one surface to another. If P and Q are cortical surfaces with

metric tensors $g_{jk}(u^i)$ and $h_{jk}(\xi^\alpha)$ in local coordinates u^i and ξ^α (i, α=1,2), the *Dirichlet energy* of the mapping $\xi(u)$ is defined as: $E(\xi) = \int_P e(\xi)(u)\, dP$, where $e(\xi)(u) = g^{ij}(u)\, \partial\xi^\alpha(u)/\partial u^i\, \partial\xi^\beta(u)/\partial u^j\, h_{\alpha\beta}(\xi(u))$ and $dP = (\sqrt{\det[g_{ij}]})du^1 du^2$. The Euler equations, whose solution $\xi^\alpha(u)$ minimizes the mapping energy, are:

$$0 = L(\xi^i) = \Sigma_{m=1\ to\ 2}\, \partial/\partial u^m\, [(\sqrt{\det[g^{ru}]})\, \Sigma_{l=1\ to\ 2}\, g^{ml}{}_{ur}\, \partial\xi^i/\partial u^l]\ (i=1,2), \qquad (12)$$

(Liseikin, 1991). The resulting (harmonic) map (1) minimizes the change in metric from one surface to the other, and (2) is again independent of the parameterizations (spherical or planar) used for each surface. The harmonic energy is therefore a functional defined on a quotient space, being invariant to the action of the reparameterization group on each surface [related algorithms for minimizing harmonic energies, invariant under re-parameterization, have been developed in level set methods for image restoration (Bertalmio et al., 2000), signal detection and smoothing on surfaces (Chung et al., 2001), in modeling liquid crystals (Alouges, 1997) and in Polyakov's formulation of string theory (Polyakov, 1987)].

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Making a Well-Resolved Average Cortical Model for a Group. The intersubject variability of the cortex is computed by first creating an average cortex for each subject group and measuring individual differences from the deformation mappings that drive the average model onto each individual. By defining probability distributions on the space of deformation transformations applied to the average template (as in Section 3), statistical parameters of these distributions are estimated from the databased anatomic data. This determines the magnitude and directional biases of anatomic variation. To do this, all 38 gyral curves for all subjects are first transferred to the parameter space (Fig. 7(e)). Next, each curve is uniformly re-parameterized to produce a regular curve of 100 points whose corresponding 3D locations are uniformly spaced. A set of 38 average gyral curves for the group is created by vector averaging all point locations on each curve. This *average curve template* (*curves* in Fig. 8(a)) serves as the target for alignment of individual cortical patterns (Thompson et al., 2000; Zeineh et al., 2001). Each individual cortical pattern is transformed into the average curve configuration using a flow field in the parameter space (Fig. 8(b); *cf*. Bakircioglu et al., 1999). By carrying a color code (that indexes 3D locations; Fig. 8(c)) along with the vector flow that aligns each individual with the average folding pattern, information can be recovered at a particular location in the average folding pattern (Fig. 8(d)) specifying the 3D cortical points mapping each subject to the average (see *Footnote 4*).

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Footnote 4. In the language of Lie algebras, corresponding 3D cortical points across the subject database are defined as the *pull-back* $D_p^*(\mathbf{r})$ (Burke, 1985) of the parameterization mappings D_p: (r,s)→(x,y,z) under the covariant vector flow $\mathbf{u}(\mathbf{r})$ that maps each subject to the average curve template. [For any smooth function D_p: $\Omega \rightarrow R^n$ and any diffeomorphic map $\mathbf{u}(\mathbf{r})$: $\Omega \rightarrow N$, there is a function on N, D_p^*: $N \rightarrow R^n$ called the pull-back of D_p by $\mathbf{u}(\mathbf{r})$, and defined by $D_p \circ \mathbf{u}$ (Burke, 1987)].

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This produces a new coordinate grid (Fig. 8(d)) on a given subject's cortex in which particular grid-points appear in the same location across subjects relative to the mean gyral pattern. By averaging these 3D positions across subjects, an average 3D cortical model can be constructed for the group. An example of this type of cortical average, based on 9 subjects with Alzheimer's disease, is shown in Fig. 8(f). The resulting mapping is guaranteed to average together all points falling on the same cortical locations across the set of brains, and ensures that corresponding features are averaged together.

Advances in Cortical Surface Matching: Related Approaches. The above mathematics is motivated by the need to (1) enforce sulcal correspondences when cortical data are averaged together, and (2) create mappings that do not depend on the way the surfaces are gridded (the covariant approach). Recent advances in level set theory and implicit PDEs promise to simplify and accelerate this process (Sapiro, 2000; Bertalmio et al., 2000; Chung et al., 2001). To solve equations that describe complex flows in a spherical parameter space, a peculiar grid structure is used, with circular wrap-around (Fig. 9), so that variables describing the flow can be stored at each node in the grid. Fast solution of the flow equations takes advantage of a class of spatial data structures, based on the Platonic solids (Fig. 9). These 'geodesic spheres' allow hierarchical gridding of the parameter space (MacDonald, 1998), and minimize distortions in grid cell area and shape towards the sphere's poles (Sahr and White, 1998).

Cortical Flattening. Minimizing distortion when flattening the cortex is a topic of intense research (Carman et al., 1995; Drury and Van Essen, 1997; Chow, 1998; Hurdal et al., 1999). This work is related to texture mapping methods in the computer graphics literature (Kanai et al., 1997; Zhang and Hebert, 1999) and theoretical work on minimal surfaces and soap films (Oprea, 1998). Pinkall and Polthier (1993) pioneered the idea of using harmonic mappings to flatten surfaces, as mathematical results exist that guarantee that grid cells are minimally distorted and do not fold over in the process (Eells and Sampson, 1964). Ingenious extensions to this method have generated conformal (angle-preserving) cortical maps using the Laplace-Beltrami operator (Angenent et al., 1999; Haker et al., 1999) or circle-packing methods (Hurdal et al., 1999). For some applications (e.g. cortical matching), covariant approaches avoid the need for isometric flattening of the cortex, by incorporating the surface metrics in the flows (Thompson et al., 2000; Chung et al., 2001). Related work by Fischl and Dale (2001) projects cortical surfaces into a spherical coordinate system while minimizing a distortion metric. They then compute a warp between two cortices by minimizing a penalty function. This consists of a curvature matching to improve the registration, an areal term to prevent folding, and a metric distortion term to favor the preservation of surface distances. All these methods aim to fulfil the goal of averaging data from corresponding cortical regions, when constructing population-based maps of the cortex. The result is an ability to analyze structural and functional data with greater statistical power (Thompson et al., 1998; Rex et al., 2000; Zeineh et al., 2001), and a method to build average cortical models whose geometry is well-resolved, and consistent with other data in a population-based atlas.

5. Brain Averaging

In making population based brain templates, a key challenge is to average individual images together so that common features of the population are reinforced. If MRI images are only globally aligned and averaged together, cortical features are washed away (Fig. 10).

Maps deforming individual cortical patterns to a group average shape can also help generate a brain template with the mean shape for a group, and with sharply defined geometry. We recently used high-dimensional transformations to create a mean image template for a group of patients with Alzheimer's disease (AD), whose anatomy is not well accommodated by existing brain atlases or imaging templates (Thompson et al., 2001). We introduce this idea now, as in later sections we will typically use an average brain coordinate space as the space in which anatomical variability is quantified.

Average Brain Templates. To make a mean image template for a group, several approaches are possible (Evans et al., 1994; Collins et al., 1994; Subsol, 1995; Grenander and Miller, 1998; Guimond et al., 1999; Thompson et al., 2000; Woods et al., 2000; Miller et al., 2002). If scans are mutually aligned using only a linear transformation (Fig. 10), the resulting average brain is blurred in the more variable anatomic regions, and cortical features are washed away. The resulting average brain also tends to exceed the average dimensions of the component brain images. By averaging geometric and intensity features separately (*cf*. Ge et al., 1995; Bookstein, 1997; Grenander and Miller, 1998; Christensen et al., 1999; Thompson et al., 2000), a template can be made with the mean intensity and geometry for a patient population. To illustrate this, we generated an initial image template for a group of Alzheimer's patients by (1) using automated linear transformations (Woods et al., 1993) to align the MRI data with a randomly selected image, (2) intensity-averaging the aligned scans, and then (3) recursively re-registering the scans to the resulting average affine image. The resulting average image was adjusted to have the mean affine shape for the group using matrix exponentiation to define average transformations (Woods et al., 1998). Images and a large set of anatomical surface models (84 per subject) were then linearly aligned to this template, and an average surface set was created for the group. Displacement maps driving the surface anatomy of each subject into correspondence with the average surface set were then computed, and were extended to the full volume with surface-based elastic warping (Thompson et al., 2000). These warping fields reconfigured each subject's 3D image into the average anatomic configuration for the group. By averaging the reconfigured images (after intensity normalization), a crisp image template was created to represent the group (Fig. 10). Note the better-resolved cortical features and sharper definition of tissue boundaries in the average images after high-dimensional cortical registration. If desired, this AD-specific atlas can retain the coordinate matrix of the Talairach system (with the anterior commissure at (0,0,0)) while refining the gyral map of the Talairach atlas to

encode the unique anatomy of the AD population. By explicitly computing matching fields that relate gyral patterns across subjects, a well-resolved and spatially consistent set of probabilistic anatomical models and average images can be made to represent the average anatomy and its variation in a subpopulation.

Uses of Average Templates. Average brain templates have a variety of uses. If functional imaging data from Alzheimer's patients are warped into an atlas template based on young normals, signals in regions with selective atrophy in disease are artificially expanded to match their scale in young normals. Biases can therefore result. If the atlas has the average geometry for the diseased group, which may include atrophy, least distortion is applied by warping data into the atlas. Since the template (in Fig. 10) also has the average affine shape for the group (Woods et al., 1998), least distortion is applied when either linear, non-linear, approaches are used. The notion of least distortion can be formulated precisely using either (1) mean vector fields (Thompson et al., 2000; Kochunov et al., 2001); (2) matrix and deformation tensor metrics (Woods et al., 2000), (3) using the L^2-norm on the Hilbert space of deformation field coefficients (Grenander and Miller, 1998; cf. Martin et al., 1994), or (4) indirectly through a continuum-mechanical operator or regularization functional that defines what it means for a distortion to be irregular (Christensen et al., 1999; Miller and Younes, 2001). These different definitions of average result from the fact that the idea of how 'far away' one anatomy is from another can be formulated with different mathematical metrics (Miller et al., 2002; see *Footnote 5*). The resulting notion of population average (a template that is least far from the individuals) is determined accordingly.

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Footnote 5. *Defining the Average Brain*. For a given nonlinear registration algorithm, and after affine components of deformation are factored out, a 'mean-field average brain template' is one for which:

$$\sum_{i=1 \text{ to } N} \int_{\Omega} \| \mathbf{u}_i(\mathbf{x}) \|^p \, d\mathbf{x}, \quad (13)$$

is minimal, when $\mathbf{u}_i(\mathbf{x})$ are the deformations mapping it onto a large set of other brains (p=1 or 2 correspond to different norms). This template is closest to all brains; on average, brains have to be warped the least 'distance' to match it. Alternatively, a 'least-distortion average brain template' is one for which:

$$\sum_{i=1 \text{ to } N} \int_{\Omega} \| L^{\ddagger} \mathbf{u}_i(\mathbf{x}) \|^p \, d\mathbf{x}, \quad (14)$$

is minimal. Here L is a (possibly covariant; see above) differential operator that measures the irregularity of the deformation field, $\ddagger$ denotes covariant differentiation with respect to the metric of the base manifold (this has no effect unless we are averaging non-flat manifolds, such as cortical surfaces, where the Christoffel symbols do not vanish). Extending these ideas to registration algorithms that use velocity fields to ensure diffeomorphic mappings (e.g., Christensen et al., 1996; see above), Miller and Younes (2001) show that:

$$\text{argmin}_{v \in V} \int_{\Omega \times [0,1]} \| L\mathbf{v}(\mathbf{x}, t) \|^2 \, d\mathbf{x} \, dt, \quad (15)$$

defines a metric on the space of diffeomorphisms, where V is the space of all velocity fields (paths) that deform the reference anatomy at t=0 onto a target anatomy at time t=1. In their formulation, a mean brain template would be one for which the following average energy is minimized:

$$\sum_{i=1 \text{ to } N} \int_{\Omega} \| L(\mathbf{v}_i(\mathbf{x}, t)) \|^2 \, d\mathbf{x}, \quad (16).$$

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As a result, average brain image templates may be defined in various different ways. The one in Figure 10 has the mean geometry *and mean intensity* for a group (Thompson et al., 2000). Kochunov et al. (2001) extended this idea to optimize the geometry of an individual image (the average of 27 MRI scans of the same subject mentioned in Section 2; Holmes et al., 1998). The individuality of brain shape was removed by first deforming this high-resolution template to 30 brains, and applying the mean deformation field to the template. Interestingly, automated registration approaches were able to reduce anatomic variability to a statistically greater degree if this specially-prepared image template was used as a registration target (Kochunov et al., 2001). With smaller deformations, local minima of the registration measure may be avoided. Convergence may also be faster, as the parameter space is searched for an optimal match. This optimality of average brain templates may help in normalizing individual brains (Fig. 11), and may also be advantageous when databases are mined for information using nonlinear registration as an information source (Thompson et al., 2000).

6. Atlas Statistics: Probabilistic Atlases

Once anatomic data are aligned with an average brain template, or atlas, a variety of statistics and maps can be computed. Some of these reflect the variability of different anatomic features in the atlas coordinate system. Features of interest include variations in gray matter distribution, structural asymmetry, incidence of sulci, and gyral patterning; they may also include rates of brain change in developing and diseased subpopulations. The result is a *probabilistic atlas* (Mazziotta et al., 1995, 2001; Thompson et al., 1997, 2000, 2001; Chiavaras et al., 2001) that provides normative criteria to detect abnormal anatomy in an individual or group. Disease-related differences, such as altered asymmetries, or gray matter deficits, can also be mapped, using the atlas as a reference standard. With appropriate statistical models, the effects of aging, medication and genetics on brain structure and brain change can be gauged in whole populations.

Mapping Anatomic Variability. As noted in Section 3, maps of anatomic variability can help assess structural abnormalities in an individual or group, by encoding what normal variations are likely to be. By using cortical pattern matching to identify corresponding cortical locations in 3D space, rather than simple image averaging (Fig. 10(a),(b)), deformation maps can be recovered mapping many individual subjects into gyrus-by-gyrus correspondence with the average cortex (Fig. 10(e)). Anatomic variability can thus be defined at each point on the average cortical mesh as the root mean square magnitude of the 3D displacement vectors, assigned to each point, in the surface maps from individual to average. This variability pattern is visualized as a color-coded map (Fig. 10(g)). This map shows the anatomic differences, due to gyral pattern variation, that remain after affine alignment of MR data into a brain template with the mean shape and intensity for the group.

Deformation-Based Morphometry. Deformations that align individual anatomies with an atlas standard can be analyzed to detect systematic differences in anatomy (a technique called 'deformation-based morphometry'; Thompson et al., 1997; Ashburner et al., 1999; Gaser et al., 1999; Ashburner, 2001; Good et al., 2001). The deformation fields contain detailed information on individual morphometry, and their statistics can be stored in an atlas. Depending on whether these fields are stored as 3D deformation *vectors* (Thompson et al., 1997; Cao and Worsley, 1999), as *tensors* (Davatzikos et al., 1996; Thompson et al., 2000; Pettey and Gee, 2001; Section 8) or as a set of *basis function coefficients* that parameterize the nonlinear warp (Csernansky et al., 1999; Ashburner, 2001), the analysis of structural differences proceeds a little differently (see also Good et al., 2001). Because of their utility in applying atlases to understand disease, we describe these approaches next (see Thompson et al., 2001, for a more detailed review).

Random Vector Fields. In a *random vector field* approach (Thompson et al., 1997; Cao and Worsley, 1999), affine components of the deformation fields are first factored out. After this, the deformation vector required to match the structure at position $\mathbf{x}$ in the average cortex with its counterpart in subject *i* can be modeled as:

$$\mathbf{W}_i(\mathbf{x}) = \boldsymbol{\mu}(\mathbf{x}) + \boldsymbol{\Sigma}(\mathbf{x})^{1/2}\boldsymbol{\varepsilon}_i(\mathbf{x}). \quad (17)$$

Here $\boldsymbol{\mu}(\mathbf{x})$ is the mean deformation vector for the population (which approaches the zero vector for large *N*), $\boldsymbol{\Sigma}(\mathbf{x})$ is a non-stationary, anisotropic covariance tensor field estimated from the mappings, $\boldsymbol{\Sigma}(\mathbf{x})^{1/2}$ is the upper triangular Cholesky factor tensor field, and $\boldsymbol{\varepsilon}_i(\mathbf{x})$ can be modeled as a trivariate random vector field whose components are independent zero-mean, unit variance, stationary random fields. This 3D probability distribution makes it possible to visualize the principal directions (eigenvectors) as well as the magnitude of gyral pattern variability, as a 'tensor map' (Fig. 12(b)). These characteristics are highly heterogeneous across the cortex. For any desired confidence threshold α, 100(1-α)% *confidence regions* for possible locations of points corresponding to $\mathbf{x}$ on the average cortex are given by nested ellipsoids $\mathbf{E}_{\Theta(\alpha)}(\mathbf{x})$ in displacement space (Fig. 12(b); Thompson et al., 1996; Thirion et al., 1999; Cao and Worsley, 1999). The shape of these ellipsoids is:

$$\mathbf{E}_{\Theta}(\mathbf{x}) = \{\boldsymbol{\mu}(\mathbf{x}) + \Theta[\boldsymbol{\Sigma}(\mathbf{x})]^{-1/2}\mathbf{p} : \mathbf{p} \in B(\mathbf{0};1)\}, \quad (18)$$

where $\mathbf{B}(\mathbf{0};1)$ is the unit ball in $\mathbb{R}^3$, and

$$\delta(\alpha) = [[N(N-3)/3(N^2-1)]^{-1} F_{\alpha,3,N-3}]^{1/2}, \quad (19)$$

where $F_{\alpha,3,N-3}$ is the critical value of the F distribution such that $\Pr\{F_{3,N-3} \geq F_{\alpha,3,N-3}\} = \alpha$ and N is the number of subjects.

Detecting Group Anatomic Differences with Random Fields. This confidence limit representation of anatomy can also detect group differences in brain structure. The significance of a difference in brain structure between two subject groups (*e.g.*, patients and controls) of N_1 and N_2 subjects is assessed by calculating the sample mean and variance of the deformation fields (j=1,2):

$$\mathbf{W}^{\mu}_{j}(\mathbf{x}) = \sum_{i=1 \text{ to } Nj} \mathbf{W}_{ij}(\mathbf{x}) / N_j$$
$$\mathbf{\Sigma}(\mathbf{x})=(1 / [N_1+N_2-2])\{ \sum_{j=1 \text{ to } 2} \sum_{i=1 \text{ to } Nj} [\mathbf{W}_{ij}(\mathbf{x})- \mathbf{W}^{\mu}_{j}(\mathbf{x})][\mathbf{W}_{ij}(\mathbf{x})- \mathbf{W}^{\mu}_{j}(\mathbf{x})]^{\mathbf{T}}\}. \quad (20)$$

and computing the following statistical map (Thompson et al, 1997; Cao and Worsley, 2001):

$$T^2(\mathbf{x})= \{N_1N_2 / (N_1+N_2) (N_1+N_2-2)\} [\mathbf{W}^{\mu}_{2}(\mathbf{x}) - \mathbf{W}^{\mu}_{1}(\mathbf{x})]^{\mathbf{T}} [\mathbf{\Sigma}(\mathbf{x})]^{-1}[\mathbf{W}^{\mu}_{2}(\mathbf{x}) - \mathbf{W}^{\mu}_{1}(\mathbf{x})], \quad (21)$$

Under the null hypothesis, $(N_1+N_2-2)T^2(\mathbf{x})$ is a stationary Hotelling's T^2-distributed random field. At each point, if we let $\nu=(N_1+N_2-2)$ and we let the dimension of the search space be d=3, then:

$$F(\mathbf{x})=((\nu-d+1)/d)T^2(\mathbf{x}) \sim F_{d,(\nu-d+1)}. \quad (22)$$

In other words, the field can be transformed point-wise to a Fisher-Snedecor F distribution (Thompson et al., 1997), and these statistics of abnormality can be plotted in color across the cortex (Fig. 12(c)). To obtain a p-value for the effect that is adjusted for the multiple comparisons involved in assessing a whole field of statistics (cf. Friston et al., 1995; Holmes et al., 1996), Cao and Worsley (1999) examined the distribution of the global maximum T^2_{max} of the resulting T^2-distributed random field under the null hypothesis. Alternatively a significance value for the whole experiment can be assigned by estimating their fraction of the statistical map that exceeds any threshold by permutation (Holmes et al., 1996; Bullmore et al., 1999; Sowell et al., 1999). This non-parametric approach avoids assumptions about the spatial autocorrelation of the process, and has been widely used in functional imaging analyses (e.g. Holmes et al., 1996). Subjects are randomly assigned to groups and the distribution of accidental clusters is tabulated empirically. We have recently used this approach to detect developmental changes in brain asymmetry and gray matter distribution, as well as gray matter loss in Alzheimer's disease and schizophrenia (see Sections 7, 8).

Mapping Brain Asymmetry. By analysis of variance in 3D deformation fields that match different subjects' anatomies, it is also possible to map patterns of brain asymmetry. To do this, we differentiate intra-subject (between hemisphere), inter-subject, and inter-group contributions to brain variation in human populations, and again we detect significant differences using null distributions for features in Hotelling's T^2 random fields. Mapping brain asymmetry in a group is an interesting application (Watkins et al., 2001), as asymmetry is linked with functional lateralization (Strauss *et al.*, 1983), handedness (Witelson, 1989), language function (Davidson and Hugdahl, 1994), and is thought to be diminished in some diseases (cf. Kikinis et al., 1994, Narr et al., 2001). Although the mappings computed so far specify the set of cortical points that correspond across subjects, an average map of asymmetry cannot be computed without an additional set of mappings to define the points that correspond across hemispheres. To do this, all left hemisphere sulcal curves are projected into the cortical parameter space, reflected in the vertical axis, and averaged with their flattened counterparts in the right hemisphere, to produce a second *average curve template*. Color maps (as in Fig. 8(c)) representing point locations in the left and right hemispheres are then subjected to a second warp, or flow, that transforms corresponding features in each hemisphere to the same location in parameter space. 3D deformation fields can then be recovered matching each brain hemisphere with a reflected version of the opposite hemisphere (cf. Thompson et al., 1998; Thirion et al., 1998; Gerig et al., 2001; Wang et al., 2001). These parameter flows are advantageous in that the asymmetry fields are also *registered*; in other words, asymmetry measures can be averaged

across corresponding anatomy at the cortex. This is not necessarily the case if warping fields are averaged at the same coordinate locations in stereotaxic space (cf. Fig. 10(a)). The pattern of mean brain asymmetry for a group of 20 subjects is shown in Fig. 13. The resulting asymmetry fields $\mathbf{a}_i(\mathbf{r})$ (at parameter space location $\mathbf{r}$ in subject i) were treated as observations from a spatially-parameterized random vector field, with mean $\boldsymbol{\mu}_a(\mathbf{r})$ and a non-stationary covariance tensor $\boldsymbol{\Sigma}_a(\mathbf{r})$ (Fig. 13(c)). The significance α of deviations from symmetry can be assessed using a T^2 or F statistic that indicates evidence of significant asymmetry in cortical patterns between hemispheres:

$$\alpha(\mathbf{r}) = F_{3,N-3}^{-1}\left([(N-3)/3(N-1)]T^2(\mathbf{r})\right) \text{ where } T^2(\mathbf{r}) = N[\boldsymbol{\mu}_a(\mathbf{r})^T \boldsymbol{\Sigma}_a^{-1}(\mathbf{r})\, \boldsymbol{\mu}_a(\mathbf{r})]. \quad (23)$$

Using this asymmetry mapping technique, we recently observed that brain asymmetry appears to increase during childhood and adolescence (Sowell et al., 2001). There may also be significant asymmetries in the degree to which genes affect brain structure (Thompson et al., 2001). Encoded knowledge on the statistics of brain asymmetry can also help detect departures from normal asymmetry and even the emergence of lesions (sometimes termed *'dissymmetry'*: see Thirion et al., 2000; Joshi et al., 2001).

Tensor-Based Morphometry. Tensor-based morphometry is related approach for detecting morphometric differences in a population, based on the deformation maps, or warping fields, that align each individual dataset with an atlas standard (Davatzikos et al., 1996; Machado and Gee, 1998). The local deformation tensor is a matrix containing the local derivatives of the warping field, and it can be used to tell whether a structure is larger or smaller relative to an atlas. Although the deformation tensor also contains information on the principal directions in which a structure is compressed or enlarged relative to an atlas, for simplicity, its determinant (also called the Jacobian) is often used instead. This is a single number reflecting whether a structure is smaller or larger than the atlas, and by how much. Essentially it is a dilation factor, expressing the ratio of a structure's size in a specific individual to its counterpart in the atlas. Gaser et al. (1999, 2001) have employed these dilation maps to localize morphometric differences in the ventricles, as well as thalamic and temporal regions, in a cohort of patients with schizophrenia (N=160; cf. Andreasen et al., 1994). Studholme et al. (2001) located points where voxel-level difference in the Jacobian occurred between groups of patients with fronto-temporal dementia, Alzheimer's disease, and semantic dementia. This indicated spatially-consistent shape differences induced by each particular disease. Davatzikos et al. (1996) and Pettey and Gee (2001) employed a similar approach to localize differences between males and females in the anatomy of the *corpus callosum* (a controversial topic reviewed in Thompson et al., 2001; see also Bermudez and Zatorre, 2001). The use of tensor maps to localize brain growth in children and anatomical change in dementia is discussed in Section 8.

Specialized Approaches for Detecting Cortical Differences. Several conventional approaches for signal detection (and enhancement) in functional images are based on mathematics that describes the distribution of features in random fields derived from images (e.g. SPM; Worsley et al., 1994a,b, 2000; Friston et al., 1995; Lange, 1996). These statistical equations become even more complicated when the data lie on curved manifolds such as the cortex (Goebel, 2000; Jones et al., 2000; Taylor and Adler, 2001; Andrade, 2001). Specifically, if cortical data are flattened, the spatial autocorrelation of the data in flat space will depend to some degree on the local parameterization tensor (or distortion) involved in flattening the surface.

This apparent barrier, however, can be turned into an advantage: if a surface model is available, it is possible to selectively enhance signals in the cortex, by searching and filtering data within the surface only (Jones et al., 2000; Chung et al., 2001). For functional activations, as well as for structural attributes of thickness, asymmetry and shape, the surface null distributions can be estimated for clusters exceeding a given height and spatial extent, and the total spatial extent of these clusters, as these help in detecting subtle effects. To estimate significance values for these maps, the roughness tensor, Λ (or its inverse, the smoothness tensor, $S=\Lambda^{-1}$), is crucial (Poline et al., 1995; Kiebel et al., 1999); it is defined as the covariance matrix of the partial derivatives of the process along each of the D coordinate axes, with variances $\mathrm{Var}[\partial X/\partial x_i]$ on the diagonal and off-diagonal elements $\mathrm{Cov}[\partial X/\partial x_i, \partial X/\partial x_j]$. Usually the smoothness is calculated not from the data itself, which may contain a physiological signal, but from the residuals after fitting a linear statistical model which removes linear effects of the experimental parameters. The roughness tensor of the process is not

likely to be stationary within the cortical surface, which can complicate the application of standard results in Gaussian field theory (Worsley et al., 1999). To alleviate this problem, a partial differential equation can be run:

$$g^{ij}(\partial^2\mathbf{u}/\partial r^i\partial r^j) + \partial/\partial u^j(S^{ij})\mathbf{u}_i i = 0 \qquad (24)$$

in the parameter space of the group average cortex. This generates a deformed grid $\mathbf{u}(\mathbf{r})$ whose deformation gradient tensor approximates the smoothness tensor S^{ij} of the normalized residuals of the data on the surface (here g^{ij} is the contravariant metric tensor of the grid). If the smoothness tensor has non-zero curvature (and is therefore not realizable as a deformation tensor), the deformation gradient approximates it in the Frobenius matrix norm. Relative to this new computational grid, the residuals become stationary and isotropic, and *p*-values for effects, such as gray matter reductions can be evaluated. This approach for detecting statistical effects in images is known as *statistical flattening* (which is to be distinguished from cortical flattening); it can be achieved using the Nash Embedding theorem (Worsley et al., 1999) or by running the above PDE on the data (Thompson et al., 2001). In a related approach, cortical signals can be detected more powerfully by smoothing data using covariant filters on the cortical surface. This technique is analogous to data 3D data smoothing in volumetric PET and fMRI studies, and is under investigation in the computer vision and image restoration literature (Sapiro, 2001; Bertalmio et al., 1999; see also Thompson et al., 2000). To increase the detection sensitivity to interesting functional and structural effects, a Laplace-Beltrami flow, induced by the Laplace-Beltrami operator $\nabla^2_{LB}I$ can be run in the cortical parameter space. This produces a scale-space of diffused data $I(\mathbf{x}, t)$ (Nielsen et al., 1994; Worsley et al., 1996; Sochen et al., 2000; Chung et al., 2001) on the cortex, which acts as a pre-filter to enhance detection of effects at different scales (Huiskamp, 1991):

$$I(\mathbf{x}, t_{n+1}) = I(\mathbf{x}, t_n) + Dt.\nabla^2_{LB}I(\mathbf{x}, t_{n+1}) \qquad (25)$$

In this process, covariant derivatives on the cortical manifold are computed from the gradients of the base vectors on a logical grid in parameter space (cf. Section 4). The resulting ability to adaptively filter data on the cortical sheet maximizes the statistical power to detect changes and differences in cortical structure and function in a population atlas, including diffuse effects across the cortex that may emerge in a population.

7. Applications to Development and Disease

Gray Matter Loss in a Diseased Population. The population-based atlasing approaches introduced so far have been applied to study brain structure in Alzheimer's disease (Thompson et al., 2000a,b; Mega et al., 1999), chronic, first-episode, and childhood-onset schizophrenia (Narr et al., 2000, 2001a,b; Cannon et al., 2001), fetal alcohol syndrome (Sowell et al., 2001), and brain changes during childhood and adolescence (Thompson et al., 2000, 2001; Sowell et al., 2001a,b; Blanton et al., 2001).

An interesting application is in visualizing the average profile of gray matter loss across the cortex in Alzheimer's disease, based on a large number of subjects at a specific stage in the disease. First we describe a cross-sectional study in which each subject is imaged once; longitudinal data are described in the next section. Gyral pattern variation makes it difficult to make inferences about where exactly gray matter is lost in a group. If gray matter maps are directly averaged together in stereotaxic space (e.g., Fig. 10(a)), it is difficult to localize results to specific cortical regions. To address this, we used cortical pattern matching to help compute group averages and statistics. First, we segmented all images in the database with a previously validated Gaussian mixture classifier. Maps of gray matter, white matter, cerebro-spinal fluid and a background class were created for each subject (Fig. 9). The proportion of gray matter lying within 15 mm of each cortical point was then plotted as an attribute on each cortex, and aligned across subjects by projecting it into flat space (Fig. 8(c)) and warping the resulting attribute field with the elastic matching technique (as in Fig. 8(d)). (Again, the gray matter proportion can be thought of as a scalar attribute $G(\mathbf{r})$ defined in the cortical parameter space, which can be subjected to a flow field $\mathbf{u}(\mathbf{r})$ to compensate for gyral pattern differences). By averaging the aligned maps, and texturing them back onto a group average model of the cortex, the average magnitude of gray matter loss was computed for the Alzheimer's disease population (Fig. 14; Thompson et al., 2000). Regions with up to 30% reduction in gray matter were sharply demarcated from adjacent regions with little or no loss. The group effect size was measured by attaching a field

of t statistics, $t(\mathbf{r})$, to the cortical parameter space, and computing the area of the t field on the group average cortex above a fixed threshold ($p < 0.01$, uncorrected). For groups that are not demographically matched, more sophisticated regression models could be applied, resulting in F fields that indicate the significance of the overall fit, and of how individual model parameters help explain the loss. In a multiple comparisons correction, the significance of the overall effect was confirmed to be $p < 0.01$, by permuting the assignment of subjects to groups 1,000,000 times.

8. Dynamic Brain Maps

Dynamic Brain Change. Everyone's brain shrinks with age, and not in a uniform way. Diseases such as Alzheimer's cause changes in the overall rates and patterns of brain change. Population-based atlases can store key statistics on the rates of these brain changes. These are especially relevant to the understanding of development (Lange et al., 1997) as well as relapsing-remitting diseases such as multiple sclerosis (Guttmann et al., 1995; Thirion et al., 1997; Rey et al., 1999; Collins et al., 2001; Welti et al., 2001) and tumor growth (Haney et al., 2001a,b). They can provide normative criteria for early brain change in patients with dementia (Jernigan et al., 1991; DeCarli et al., 1992; Janke et al., 2001; Thompson et al., 2001), with mild cognitive impairment (Studholme et al., 2001), or in those at genetic risk for Alzhemer's disease (Small et al., 2000). An interesting application is the compilation of dynamic maps to characterize diseases with childhood or adolescent onset, which we illustrate next.

In a developmental application (Thompson et al., 2001; Fig. 15), the gray matter mapping procedure, described above, was applied to longitudinal MRI data from 12 schizophrenic patients and 12 adolescent controls scanned at both the beginning and end of a 5-year interval. The goal was to estimate the average rate of gray matter loss throughout the cortex, by matching cortical patterns and comparing changes in disease with normal changes in controls. Cortical models and gray matter measures were elastically matched first within each subject across time, to compute individual rates of loss, and then flowed into an average configuration using flat space warping (Fig. 8(d))). The resulting maps (Fig. 15) showed dynamic loss of gray matter in superior parietal, sensorimotor and some frontal brain regions (up to 5% annually; Fig. 15(a)). Group differences were highly significant ($p < 0.01$, *permutation test;* Fig. 15(b)), relative to healthy controls and non-schizophrenic controls matched for medication and IQ, and were linked with psychotic symptom severity (for details, see Thompson et al., 2001).

Tensor Maps of Brain Change. Maps of brain change over time can also be based on a deformation mapping concept. In this approach, a 3D elastic deformation is calculated. This deformation, or warping field, drives an image of a subject's anatomy at a baseline timepoint to match its shape in a later scan. Image warping algorithms have evolved over many years (Toga, 1998). Now mappings can be calculated in a very exact way that matches a large number of the key functional and anatomic elements in the scans to be matched. This results in a very complex transformation, often with up to a billion parameters, from which local volume changes in tissues can be calculated (Miller *et al.*, 1993; Christensen *et al.*, 1993, 1995, 1996; Collins et al., 1994, 1995; Davatzikos, 1996; Thompson and Toga, 1996; Davis et al., 1996, 1997; Bro-Nielsen and Gramkow, 1996; Dupuis et al., 1998; Gee *et al.*, 1993, 1995, 1998; Freeborough and Fox, 1998; Thompson *et al.*, 1999, 2001; Cachier *et al.*, 1999; Janke *et al.*, 2001). In capturing brain change, deformation-based methods can be complementary to voxel-based morphometric methods (Ashburner and Friston, 2000; Good et al., 2001), and methods that estimate whole brain atrophic rates (Subsol et al., 1997; Calmon and Roberts, 2000; Collins et al., 2001; Smith et al., 2001). Voxel-based methods typically use a simple pixel-by-pixel subtraction of scan intensities registered rigidly across time. Deformation methods, however, can distinguish local from global effects, and true tissue loss from shifts in anatomy. These can confound image subtraction methods.

Mapping Growth Patterns. We recently developed a deformation-based approach to detect an anterior-to-posterior wave of growth in the brains of young children scanned repeatedly between the ages of 3 and 15 (Thompson et al., 2000). Parametric surface meshes were built to represent anatomical structures in a series of scans over time, and these were matched using a fully volumetric deformation. Dilation and contraction rates, and even the principal directions of growth, can be derived by examining the eigenvectors of the deformation gradient tensor, or the local Jacobian matrix of the transform that maps the earlier anatomy onto the later one (see Fig. 16). Applications include measuring the statistics of brain growth (Thompson et al., 2000), and measuring tumor response to novel chemotherapy

agents (Haney et al., 2001). By building probability densities on registered tensor fields (e.g. Thompson et al., 2000; Chung et al., 2001), a quantitative framework can be established to detect normal and aberrant brain change, and its modulation by medication in clinical trials.

Mathematical Details. Deformation-based methods to track brain change have often been based on continuum mechanics, which describes physical models of elastic or fluid bodies (reviewed in Toga, 1998; Thompson and Toga, 2000; *cf*. Freeborough and Fox, 2000; Haney et al., 2001a,b; Chung et al., 2001). The 3D shape of one brain, imaged with MRI at one time-point, is reconfigured to match its shape in a later image (intensity changes over time may also be modeled; q.v. Joshi et al., 2001). A complex 3D deformation field is computed that matches large numbers of surface, curve, and point landmarks in the two brains (see Thompson *et al.*, 2000 for details, and a review of similar methods by other groups). Important anatomic and functional interfaces are matched up when one scan is deformed into the shape of the other. Parametric mesh models of brain structures are used to drive a 3D deformation vector map $U: \mathbf{x} \mapsto \mathbf{u}(\mathbf{x})$ which is derived from the Navier equilibrium equations for linear elasticity:

$$\mu \nabla^2 \mathbf{u} + (\lambda+\mu) \nabla (\nabla \cdot \mathbf{u}(\mathbf{x})) + \mathbf{F}(\mathbf{x}-\mathbf{u}(\mathbf{x})) = \mathbf{0}, \forall \mathbf{x} \in R \qquad (26).$$

All the terms in this equation just describe forces and distortions in a 3D material, in which the image considered to be embedded. R is a discrete lattice representation of the scan to be transformed, $\nabla \cdot \mathbf{u}(\mathbf{x}) = \sum \partial u_j / \partial x_j$ is the divergence, or cubical dilation of the medium, ∇^2 is the Laplacian operator which measures the irregularity of the deformation, $\mathbf{F}(\mathbf{x})$ is the internal force vector, and Lamé's coefficients λ and μ refer to the elastic properties of the medium. Matching of cortical surfaces, across time and subsequently across subjects (for data averaging) can also be enforced. Mappings based on high-dimensional elastic and fluid models can recover extremely complex patterns of change (Fig. 17; see also Freeborough and Fox, 1998; Christensen et al., 1996; Rey et al., 1999); their mathematics is reviewed elsewhere (Thompson et al., 2000).

Population-Based Atlasing of Brain Change. In different individuals, growth processes occur in anatomies that are geometrically different. Additional warping techniques are needed to compare growth profiles across subjects. This additional warping is needed to compute average profiles, and to define statistical differences in rates of growth or loss. Mathematically, if $U^i(\mathbf{x},t_i)$ is the 3D displacement vector required to deform the anatomy at position $\mathbf{x}$ in subject i at reference time 0 to its corresponding homologous position at time t_i, then a linear approximation the local rate of volumetric growth (Chung et al., 2001) can be written in terms of the identity tensor and displacement gradient tensor as:

$$\Lambda^i(\mathbf{x}) = \partial J^i / \partial t = det\,(I + \nabla U^i) / t_i, \quad (27)$$

If A^i is the secondary deformation mapping transforming the baseline anatomy of individual i onto the atlas ('*Warping Field'*, in Fig. 18), then the set of registered growth maps $\Lambda^i(A^i(\mathbf{x}))$ (*shown in the final panel of Figure 18*) can be treated as observations from a spatially-parameterized random field, whose mean and variance can be estimated. Statistical effects of age, gender, genotype or medication can then be detected using random field theory to produce statistical maps (Thompson et al., 2001; Ashburner, 2001).

Improved Dynamic Models. In developing dynamic atlases for clinical applications, there is a particular interest in modeling developmental processes that speed up or slow down. Diseases may accelerate, or they may be attenuated by therapy. If individuals are scanned more than twice over large time-spans, this presents the opportunity for more accurate detection of brain change, and encoding of these changes in a group atlas. To compare growth patterns in different groups of subjects, the general linear model can be used to analyze the registered growth profiles (or degenerative profiles). For the *i*th individual's *j*th measure we have:

$$Y_{ij} = f(\mathrm{Age}_{ij}, \underline{\beta}) + \varepsilon_{ij} \qquad (28).$$

Here Y_{ij} signifies the outcome measure at a voxel or surface point, such as growth or tissue loss, $f()$ denotes a constant, linear, quadratic, cubic, or other function of the individual's age for that scan, and $\underline{\beta}$ denotes the regression/ANOVA coefficients to be estimated. Age (Age_{ij}) may be replaced by time from the onset of disease, the start of medication, or the time from the onset of puberty (Giedd et al., 1999). This flexibility will allows one to temporally register dynamic patterns using criteria that are expected to bring into line temporal features of interest that appear systematically in a group (Janke et al., 2001). In the above model, the coefficient vector, $\underline{\beta}$, is assumed to be constant, i.e. a fixed effect. The ε_{ij} are assumed normally distributed and uncorrelated both between and within individuals. If multiple scans are available over time, a random effects model can also model brain changes in a population:

$$Y_{ij} = \alpha_i + f(Age_{ij},\underline{\beta}) + \varepsilon_{ij} \quad (29).$$

Here the model is the same as the General Linear Model except for the α_i term, which is called a *random effect* (Pinheiro and Bates, 2000). It describes the correlation between an individual's multiple scans. Random effects models may also be fitted with *correlated* errors (Davidian and Giltinan, 1995; Verbeke and Molenberghs, 1997). If this is done, ε_{ij} and ε_{ik} (k not equal to j) are assumed correlated with the correlation a function of the time elapsed between the two measurements (Giedd et al., 1999). In models whose fit is confirmed as significant, e.g. by permutation, loadings on nonlinear parameters may be visualized as attribute maps $\underline{\beta}(\mathbf{x})$. This reveals the topography of accelerated or decelerated brain change (Thompson *et al.*, 2001). The result is a formal approach to assess whether, and where, brain change is speeding up or slowing down. This is key feature in developmental or medication studies, and a key element of developmental atlases that are currently being built.

9. Genetic Brain Maps

One of the most exciting frontiers of brain imaging is its linkage with genetic data in large human populations. Linking brain structure and genotype is important to understand:

(1) the normal heritability of brain structure (Oppenheim et al., 1989; Bartley et al., 1997; Biondi et al., 1998; Pfefferbaum et al., 2000; LeGoualher et al, 2000; Baare et al., 2001; Thompson et al., 2001), and

(2) how deficits are inherited in diseases where there are known genetic risks (e.g. Alzheimer's, schizophrenia).

These genetic studies can be set up in several ways. If a candidate marker, or risk gene, is known (e.g. apolipoprotein E, or ApoE, in Alzheimer's disease; Roses, 1997), an individual's genetic status can be used as a covariate to mine for effects of the risk gene on brain structure or function (Small et al., 2000; Laakso et al., 2000; Reiman et al., 2001). For other diseases that are polygenic, candidate markers may be elusive (e.g., schizophrenia, autism). In these cases, genetic effects on brain structure may be tested using twin, familial, or discordance designs (see Lohmann et al., 1999; Thompson et al., 2001, Cannon et al., 2001, Narr et al., 2001; Styner and Gerig, 2001; Molloy et al., 2001, for examples).

Genetic Influences on Brain Structure. The few existing studies of brain structure in twins suggest that the overall volume of the brain itself (Tramo et al., 1998) and some brain structures, including the corpus callosum (Oppenheim et al., 1989; Pfefferbaum et al., 2000) and ventricles, are somewhat genetically influenced, while gyral patterns, observed qualitatively or by comparing their 2D projections, are much less heritable (Bartley et al., 1997; Biondi et al., 1998; cf. Le Goualher et al., 2000).

Genetic Brain Maps. In a recent approach, we developed a brain atlas based on twins to determine genetic influences on brain structure (Thompson et al., 2001; Plomin and Kosslyn, 2001). We compared the average differences in cortical gray matter density (Wright et al., 1995; Sowell et al., 1999; Thompson et al., 2000; Ashburner and Friston, 2000; Good et al., 2001) in groups of unrelated subjects, as well as in dizygotic (DZ) and monozygotic (MZ) twins. This approach is known as the *classical twin design*. Although both types of twins share gestational and postgestational

rearing environments, DZ twins share, on average, half their segregating genes, while MZ twins are normally genetically identical (with rare exceptions due to somatic mutations). Maps of intrapair gray matter differences, generated within each MZ and DZ pair, were elastically realigned for averaging across the pairs within each group, prior to intergroup comparisons. First, maps of intrapair variance and broad-sense heritability were computed using Falconer's method (Falconer, 1989) to determine all genic influences on the phenotype, at each cortical point. Heritability, which is usually denoted by h^2, is a useful statistical construct that estimates the amount of variation in a structural attribute, or a behavioral trait, that is attributable to genetic factors. It can be estimated in different ways (Feldman and Otto, 1997), but is usually defined as twice the difference between MZ and DZ intraclass correlation coefficients (see Fig. 19).

By treating the loss of variance with increasing genetic affinity as an observation from an *F*-distributed random field, we identified a genetic cascade in which within-pair correlations were highest for MZ twins, lower for DZ twin pairs, and lowest of all for unrelated subjects. Specific regions of cortex were more heritable than others. We plotted these correlations across the cortex and assessed their statistical significance. The resulting maps indicate a successively increasing influence of common genetics.

Cognitive Linkages. Genetically identical twins displayed only 10-30% of normal differences (Fig. 19(a); *red and pink colors*) in a large anatomical band spanning frontal, sensorimotor, and Wernicke's language cortices. This suggests strong genetic control of brain structure in these regions. Intriguingly, the highly heritable frontal gray matter differences were also linked to Spearman's *g*, which measures successful test performance across multiple cognitive domains ($p<0.018$). Like IQ, this widely-used measure isolates a component of intellectual function common to multiple cognitive tests, and has been shown to be highly heritable across many studies, even more so than specific cognitive abilities ($h^2=0.62$, McClearn et al., 1997; *cf*. Feldman and Otto, 1997; $h^2=0.48$, Devlin et al., 1997; $h^2=0.6$-0.8, Finkel et al., 1998; cf. Swan et al., 1990; Loehlin et al., 1989; Chipuer et al., 1990; Plomin and Petrill, 1997). Genetic factors may therefore contribute to structural differences in the brain that are statistically linked with cognitive differences. The resulting genetic brain maps reveal a strong relationship between genes, brain structure, and behavior, suggesting that highly heritable aspects of brain structure may also play a fundamental role in determining individual differences in cognition (Thompson et al., 2001; Plomin and Kosslyn, 2001).

Discordance Studies. Parallel studies of heritability are also underway mapping genetic components of deficits in schizophrenia (Cannon et al., 2001; cf. Noga, 1999; Styner and Gerig, 2001). These correlational models of genetic determination (Fig. 19) are among the simplest. They can be extended to path analyses, or structural equation models widely used in population genetics, in cases where sample sizes are large enough to reliably estimate their parameters. More advanced models have also been proposed to estimate gene-environment interaction and covariance terms, when gauging genetic influences on phenotype (Neale and Cardon, 1992; cf. Loehlin, 1989; Swan et al., 1990; Chipuer et al., 1990; Plomin and Petrill, 1997; Finkel et al., 1998; Molloy et al., 2001).

The resulting techniques for genetic brain mapping represent an exciting new dimension in computational anatomy. When genetic brain maps are included in population-based atlases, they begin to shed light on familial liability and potential genetic triggers for human brain diseases (Cannon et al., 2001).

10. Subpopulation Selections

A key advantage of a population-based brain atlas is that it can be stratified, according to genetic, demographic, or therapeutic criteria, to reflect a more constrained subset of the population. Differences in a diseased population, or one with known genetic risk, can be visualized by reference to a normative standard. Normative atlases based on young normals can store a rich variety of structural and functional data (Mazziotta et al., 1995, 2001). These atlases have recently been expanded to incorporate data from elderly and developing populations (Paus et al., 1999; Thompson et al., 2000, 2001; Chung et al., 2001), as well as data from the whole gamut of imaging devices (Toga and Mazziotta, 1996; Roland and Zilles, 1996). Additional disease-specific atlases are under development for populations with Alzheimer's disease (Mega et al., 1997, 1999; Thompson et al., 2000, 2000; Dinov et al., 2001), whose brain morphology is not well-accommodated by existing templates. The ability to stratify these atlases by demographic criteria shows promise in

uncovering gender effects and interactions in disease (Fig. 5; Narr et al., 2000). The ability to select subpopulations from the database makes it possible to compare different groups with similar or overlapping symptom profiles (Thompson et al., 2001). This is of particular interest in populations of patients with complex disorders such as schizophrenia. As cohort studies are performed, the growing atlas provides a basis to contrast chronically-medicated and first-episode patients (Narr et al., 2001), childhood-onset and adult patients (Rapoport et al., 1999; Thompson et al., 2001), schizoaffective and bipolar patients, patients receiving different medications, and even family members with difference genetic risks (Cannon et al., 2001). The incorporation of discordant twins (Noga, 1999; Cannon et al., 2001) and familial pedigree data (Kaprio et al., 1990) into population atlases shows enormous promise for understanding disease transmission in human populations. The associated tools for mapping genetic influences on brain structure (Lohmann et al., 1999; Thompson et al., 2001; Styner and Gerig, 2001) are also beginning to offer the potential to map inheritance patterns, and identify brain regions with specific genetic risk. Informatics projects that link data from international genome mapping (Collins, 2001) and brain mapping projects (Huerta and Koslow, 1996) will also allow atlases to be more easily mined for genotype-phenotype relationships. This will facilitate the quest for specific genetic markers and quantitative trait loci that confer liability for a particular disease, personality trait, or intellectual ability (Gottesman et al., 2000; Plomin and Kosslyn, 2001).

Data Mining. The growth of brain imaging databases also presents opportunities to determine unforeseen patterns in large datasets with exploratory data mining or data profiling techniques (Megalooikonomou et al., 2000). Exploratory techniques such as unsupervised learning or independent components analysis (ICA; Bell and Sejnowki, 1995; Hyvärinen et al., 2001) have been applied fruitfully for source identification in EEG and fMRI time-series (Makeig et al., 1996; McKeown et al., 1998). These techniques use information theory (Shannon, 1948; Hyvärinen et al., 2001) and neural networks to uncover fundamental factors that govern variation in datasets. They often attempt to find a projection of the entire dataset, using a 'demixing' matrix, or even a nonlinear mapping, that maximizes the entropy of the data or minimizes the mutual information (Bell and Sejnowski, 1995). The output is a clustering of the data, or representation in terms of latent variables or factors, which explain the structure of the observations and may reveal their underlying causes. In the future, data mining techniques may be applied to isolate novel patterns in population-based atlases, such as diagnostic subtypes, developmental stages, or unsuspected groupings in the data. As atlases are populated with thousands of datasets, a resurgence is likely in information-theoretic mathematical tools that extract information from images, compare disparate datasets, and detect patterns with statistical and visual power.

11. Conclusion

In this paper we presented a mathematical framework to create population-based brain atlases. This emerging field in medical imaging is already uncovering fundamental features of brain structure and function in health and disease. Brain data is so complex and variable that it is essential to rely on brain atlases, templates, and anatomical models in large-scale investigations. Deformable and probabilistic atlases can warehouse population-based data in a common 3D reference frame. They capture anatomic variability using a variety of mathematical approaches. The interest in cortical anatomy, in particular, has motivated specialized approaches to analyze its structure (Fig. 20). Finally we suggested several new directions for future atlas development. Dynamic and genetic brain maps, among other new techniques, are beginning to reveal how the brain develops, how diseases progress, and how genes affect complex patterns of brain structure. The resulting armory of tools shows enormous promise in shedding light on the complex structural and functional organization of the human brain.

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Figure Legends

Fig. 1. *Elements of a Disease-Specific Atlas.* This schematic shows the types of maps and models contained in a disease-specific brain atlas (Thompson et al., 2000; Mega et al., 2000). A diverse range of computational anatomical tools are required to generate these average brain image templates (continuum-mechanical atlas), models and maps. Disease-specific brain atlases, such as this one based on patients with Alzheimer's disease (AD), allow imaging data from diverse modalities to be compared and correlated in a common 3D coordinate space. 3D anatomical models (e.g. cortical surfaces, *bottom row*), were extracted from a database of structural MRI data from AD patients. Models of these and other structures were digitally averaged and used to synthesize an average brain template (*Continuum-Mechanical Atlas, middle*) with well-resolved anatomical features in the mean shape and size for the population (see Section 5 for details). By rotating and scaling new images to occupy the same space as this template, models of subcortical, ventricular and deep nuclear structures can be built (*lower left*). Average models for patients and controls then be used to compute average patterns and statistics of cortical variability and asymmetry (*top left*), to chart average profiles of gray matter loss in a group, and to detect atrophy in a group or individual (*probability maps; left column*). Mega et al. (1997, 1999) also fused histologic maps of *post mortem* neurofibrillary tangle (NFT) staining density, biochemical maps of beta-amyloid distribution, and 3D metabolic FDG-PET data obtained 8 hours before death, in the same patient with AD (*top middle panels*). By classifying gray and white matter (tissue classification) and unfolding the topography of the hippocampus (*right panels*), Zeineh et al. (2001) revealed the fine-scale anatomy and dynamics of brain activation during memory tasks, using high-resolution functional MRI (time course shown for activation in right parahippocampal cortex, PHC). Atlasing techniques can represent and compare these diverse datasets in a common coordinate space, enabling novel multi-subject and cross-modality comparisons.

Fig. 2. *Computing Anatomical Differences with a Deformable Brain Atlas.* When a cryosection atlas of the brain (a) is deformed to match the anatomy of an individual patient (b), here imaged with 3D MRI, there are two useful products. The first is an high-resolution anatomical template that is customized to reflect the individual's anatomy, and the second is a mathematical record of the shape differences between the atlas and the individual (warped grid, (d)). These fields can be analyzed statistically to quantify differences in brain structure and detect abnormal anatomy. The transformation of the atlas onto the target MRI is here performed by constraining functionally important surfaces to match, while extending the deformation to the full 3D volume (Thompson and Toga, 1996).

Fig. 3. *Modeling Anatomy with Surface Meshes.* The derivation of a standard surface representation for each structure makes it easier to compare anatomical models from multiple subjects. An algorithm converts a set of digitized points on an anatomical structure boundary (e.g., deep sulci (a)) into a parametric grid of uniformly spaced points in a regular rectangular mesh stretched over the surface ((b); Thompson et al., 1996). By averaging nodes with the same grid coordinates across subjects (c), an average surface is produced for the group. However, information on each subject's individual differences is retained as a vector-valued displacement map (d,e). This map indicates how that subject deviates locally from the average anatomy. The root mean square magnitude (e) of these deviations provides a variability measure whose values can be visualized using a color code (f). These maps can be stored to measure variability in different anatomic systems, including ventricular and deep sulcal (Thompson et al., 1998) surfaces. A more complex method measures cross-subject variations in gyral patterns, with a surface matching procedure that better reflects anatomical variations at the cortex (see Section 4). These maps can be stored to measure variability (f) and detect typical (or abnormal) patterns of brain structure in different anatomic systems.

Fig. 4. *Population-Based Maps of Average Ventricular Anatomy in Normal Aging and Alzheimer's Disease.* In patients and controls, 3D parametric surface meshes (Thompson et al., 1996) were used to model 14 ventricular elements (a), and meshes representing each surface element were averaged by hemisphere in each group. (b) An average model for Alzheimer's patients (*red;* AD) is superimposed on an average model for matched normal controls (*blue;* NC). Mesh averaging reveals enlarged occipital horns in the Alzheimer's patients, and high stereotaxic variability (c) in both groups. Extreme variability at the occipital horn tips also contrasts sharply with the stability of septal and temporal ventricular regions. A top view of these averaged surface meshes reveals localized asymmetry, variability, and displacement within and between groups. These subcortical asymmetries emerge only after averaging of anatomical maps in large groups of subjects.

Fig. 5. *Corpus Callosum in Schizophrenia.* [Data from Narr et al., 2000, courtesy of Katherine Narr]. Midsagittal *corpus callosum* boundaries were averaged from 25 patients with chronic schizophrenia (DSM-III-R criteria; 15 males, 10 females; age: 31.1 +/- 5.6 yrs.) and from 28 control subjects matched for age (30.5 +/- 8.7 yrs.), gender (15 males, 13 females) and handedness (1 left-handed subject per group). Profiles of anatomic variability around the group averages are also shown (*in color*) as an r.m.s. deviation from the mean. Anatomical averaging reveals a pronounced and significant bowing effect in the schizophrenic patients relative to normal controls. Male patients show a significant increase in curvature for superior and inferior callosal boundaries ($p < 0.001$), with a highly significant Sex by Diagnosis interaction ($p < 0.004$). The sample was stratified by Sex and Diagnosis and separate group averages show that the disease induces less bowing in females (*panel 1*) than in males (*panel 2*). While gender differences are not apparent in controls (*panel 3*), a clear gender difference is seen in the schizophrenic patients (*panel 4*). Abnormalities localized in a disease-specific atlas can therefore be analyzed to reveal interactions between disease and demographic parameters.

Fig. 6. *Measuring Differences in Cortical Anatomy.* Based on an individual's 3D MRI scan (a), detailed surface models of the cerebral cortex can be generated (b),(c). A template of 3D curved lines is delineated on these surfaces, capturing the morphology of the sulcal pattern. On the lateral brain surface, important functional landmarks include the central (CENT), pre- and post-central (preCENT, poCENT), superior and inferior frontal sulci (SFS, IFS), intraparietal sulcus (IP), Sylvian fissure (SF) and superior temporal sulcus (STS). Medial surface landmarks include the corpus callosum (CC), anterior and posterior calcarine (CALCa/p), parieto-occipital, subparietal, paracentral, paracingulate, and cingulate sulci, and the superior and inferior rostral sulci. A spherically-parameterized, triangulated 3D mesh represents the cortical surface; (d) shows the grid structure around the anterior corpus callosum. When the parameter space of the surface is flattened out (e), landmarks in the folded brain surface can be reidentified (e.g. IRS, SRS, etc.). (The white patch by the *corpus callosum* is where the surface model cuts across the white matter of the brain stem). To avoid loss of 3D information in the flattening, a color code is used to store where each flat map location came from in 3D, with red colors brighter where the lateral (X) coordinate is larger,

green colors brighter where the posterior-to-anterior coordinate (Y) is larger, etc. The warping of these color maps (Figs. 7,8), and the averaging of the resulting images, provides a surprising strategy for creating average cortical models for a group of subjects, and for exploring cortical pattern variation.

Fig. 7. *Cortical Pattern Matching.* Cortical anatomy can be compared, for any pair of subjects (*3D Models; top left*), by computing a 3D deformation field that reconfigures one subject's cortex onto the other (*3D Matching Field, top right*). In this mapping, gyral patterns can be constrained to match their counterparts in the target brain. To do this, flattening or inflation of the extracted cortical surface provides a continuous inverse mapping from each subject's cortex to a sphere or plane. A vector field $\mathbf{u}(\mathbf{r})$ in the parameter space can then drive the gyral pattern elements into register on the sphere (*see spherical flow*). The full mapping (*top middle*) is recovered in 3D space as a displacement vector field matching cortical regions in one brain into precise structural registration with their counterparts in the other brain. *Tensor Maps (middle and lower left):* Different amounts of local dilation and contraction (encoded in the metric tensor of the mapping, $g_{jk}(\mathbf{r})$) are required to transform the cortex into a simpler 2-parameter surface. These variations complicate the direct application of 2D warping equations for matching their features. Using a covariant tensor approach (*red box*) the regularization operator L is replaced by its covariant form $L^{\ddagger}$. Correction terms (Christoffel symbols, Γ^{i}_{jk}) compensate for fluctuations in the metric tensor of the inflation and flattening procedures. This (1) makes the matching field independent of the underlying gridding of the surface (spherical or planar), and (2) eliminates effects of metric distortions that occur in the inflation or flattening procedure.

Fig. 8. *Cortical Pattern Matching and Averaging.* A well-resolved average cortical model (*panel 6*) for a group of subjects can be created by first flattening each subject's cortical model to a 2D square (*panel 1*; see also Figs. 6 and 7). A color coded map (3) stores a unique color triplet (RGB) at each location in the 2D parameter space encoding the (x,y,z) coordinate of the 3D cortical point mapped to that 2D location. By averaging these color maps pixel-by-pixel across subjects, and then decoding the 3D colors into a surface model, a smooth cortical model (5) is produced. However, a well-resolved average model (6) is produced, with cortical features in their group mean location, if each subject's color map is first flowed (4) so that sulcal features are driven into the configuration of a 2D average sulcal template (2). The average curve set is defined by 2D vector averaging of many subjects' flattened curves. In this flow (4), codes indexing similar 3D anatomical features are placed at corresponding locations in the parameter space, and are thus reinforced in the group average (6).

Fig. 9. *Computational Grids used for Cortical Parameterization and Matching.* Cortical data can be compared from one individual to another by first imposing a spherical grid structure onto the anatomy of the cortex (Thompson et al., 1997; MacDonald, 1998; Fischl and Dale, 2001). A specialized geodesic grid structure (a) is applied to each hemisphere, and the resulting discrete, triangulated mesh can be further transformed to a plane (b). One octant of the sphere is highlighted in red. (b) is adapted from the work of Zhang and Hebert (1999), who employ the theory of harmonic mappings (Pinkall and Polthier, 1993) to project 3D surface data into the plane, with minimal metric distortion (cf. Thompson et al., 2001). In our approach (Thompson et al., 2000; Fig. 7), we match cortical features from one individual to another by computing flows that align features in spherical space (cf. Bakircioglu et al., 1999 and Fischl et al., 1999 for similar approaches). Partial differential equations are used to perform the matching. The periodic (spherical) parameter space can also be represented using a gridded square (c), in which boundary elements *1* and *1'*, *2* and *2'*, etc. are regarded as topologically adjacent (green arrows). All these grid structures are designed to allow efficient calculations on cortical data, including flow fields that match cortical anatomy across subjects (Fig. 8).

Fig. 10. *Average and Probabilistic Brain Templates.* Direct averaging of imaging data after a simple affine transform into stereotaxic space washes cortical features away ((a); Evans et al., 1994; N=305 normals; (b) shows a similar approach with N=9 Alzheimer's patients). By first averaging a set of vector-based 3D geometric models, and warping each subject's scan into the average configuration (as in Fig. 5)), a well-resolved average brain template is produced (c). Deformation vector maps (e) store individual deviations (*brown mesh*) from a group average (white surface, (d)), and their covariance fields (f) store information on the preferred directions and magnitude (g) of anatomic variability (*pink colors, large variation; blue colors, less*).

Fig. 11. *Comparing Different Registration Approaches.* The ability of different registration algorithms to reduce anatomic variability in a group of subjects (N=9, Alzheimer's patients) is shown here. Digital anatomic models for each subject were mapped into common coordinate spaces using the transformations specified in the Talairach atlas (*Tal*; Talairach and Tournoux, 1988), as well as automated affine (or first-order) and eighth-order polynomial mappings as implemented in the *Automated Image Registration* package (Woods et al., 1993, 1998, 1999). After applying each type of mapping to the models from all subjects, the residual variability of ventricular (*top row*) and deep cortical surfaces (*middle row*) and superficial sulci (bottom row), is shown as a color coded map across each structure. The color represents the 3D root mean square distance from individual models to an average model for each structure, where distance is measured to the near-point on the average mesh model (Thompson et al., 1999). As expected, polynomial transformations reduce variability more effectively than affine transformations, and both outperform the Talairach system. At the cortex, model-driven registration can be used, if desired, to explicitly match gyral patterns (Thompson et al., 2000), improving registration still further.

Fig. 12. *Mapping Cortical Shape Anomalies.* Due to individual anatomical differences, an individual subject's brain may not match the shape of an anatomical atlas, and also may deviate from an average cortical model prepared for a group (a); white mesh). However, elastic warping algorithms can apply local dilations and contractions to the average brain model, deforming its shape to match the individual anatomy so that key surfaces and landmarks correspond. These deformations also store detailed information on how specific individuals (e.g. *brown mesh*, (a)) deviate from the atlas. Mean anatomical shapes and confidence limits on normal variation (b) can be computed. If individual deviations (a) are calibrated against the probability distributions that capture normal variation, abnormality maps (c) may be generated indicating the probability of finding the anatomy in its observed configuration in a normal population. Here, in a patient with mild Alzheimer's disease, atrophic changes are easiest to detect in orbitofrontal regions where normal variation is least (*labeled F in* (b); *red colors* in (c); data from Thompson et al., 1997, 1998).

Fig. 13. *Mapping Brain Asymmetry in a Population.* The average magnitude of brain asymmetry in a group (N=20, *elderly normals*) can be assessed based on warping fields that map the cortical pattern of one hemisphere onto a reflected version of the other, and then flow the observations again so that

corresponding measures can be averaged across subjects. Variations in asymmetry are also non-stationary across the cortex (*lower left*), and a Hotelling's T^2 statistical field can be computed to map the significance of the asymmetry (*lower right*) relative to normal anatomic variations (see text for mathematical details).

Fig. 14. *Average Patterns of Cortical Gray Matter Loss in Alzheimer's Disease*. Scalar fields that represent the density of gray matter across the cortex (a) can be aligned using elastic matching of cortical patterns. A localized and highly significant loss of gray matter [(b),(c)] is revealed in temporo-parietal cortices of Alzheimer's patients relative to matched elderly controls, in a similar pattern to the metabolic and perfusion deficits seen early in the disease. If longitudinal data are available, scalar fields representing the rates of gray matter loss can also be compared (see Fig. 15).

Fig. 15. *Average Rates of Gray Matter Loss in Normal Adolescents and in Schizophrenia*. (*Left two columns*): 3D maps of brain changes, derived from high-resolution magnetic resonance images (MRI scans) acquired repeatedly from the same subjects over a 5-year time span, reveal profound, progressive gray matter loss in schizophrenia (*right column*). Average rates of gray matter loss during the 5-year period from 13 to 18 years of age are displayed on average cortical models for the group. Severe loss is observed (*red and pink colors*; up to 5% annually) in parietal, motor and temporal cortices, while inferior frontal cortices remain stable (*blue colors*; 0-1% loss). Dynamic loss is also observed in the parietal cortices of normal adolescents, but at a much slower rate. (Right three columns): These maps show the local significance of the dynamic brain change in normal adolescents, in schizophrenic subjects. By comparing the average rates of loss in disease (*middle column*) with the loss pattern in normal adolescents (*first column*), the normal variability in these changes can also be taken into account and the significance of disease-specific change can be established (*last column*). [Data from Thompson et al., 2001].

Fig. 16. *Tensor Maps of Brain Change: Visualizing Growth and Atrophy*. If follow-up (longitudinal) images are available, the dynamics of brain change can be measured with *tensor mapping* approaches (Thompson et al., 2000). These map volumetric change at a local level, and show local rates of tissue growth or loss. Fastest growth is detected in the isthmus of the corpus callosum in two young girls identically scanned at ages 6 and 7 (a), and at ages 9 and 13 (b). Maps of loss rates in tissue can be generated for the developing caudate ((c), here in a 7-11 year old child), and for the degenerating hippocampus [(d),(e)]. In (e), a female patient with mild Alzheimer's disease was imaged at the beginning and end of a 19 month interval with high-resolution MRI. The patient, aged 74.5 years at first scan, exhibits faster tissue loss rates in the hippocampal head (10% per year, during this interval) than in the fornix. These maps may ultimately help elucidate the dynamics of therapeutic response in an individual or a population (Thompson et al., 2000, 2001; Haney et al., 2001).

Fig. 17. *Deforming Anatomical Templates with Neural Nets and Continuum Mechanical Flows*. The complex transformation required to reconfigure one brain into the shape of another (Fig. 2) can be determined using neural networks (a) or continuum-mechanical models [(b),(c)], which describe how real physical materials deform. In Davis et al. (1997), each of the 3 deformation vector components, $\mathbf{u}^k(\mathbf{x})$, is the output of the neural net when the position in the image to be deformed, $\mathbf{x}$, is input to the net. Outputs of the hidden units (G_i, π_m) are weighted using synaptic weights, w_i. If landmarks constrain the mapping, the weights are found by solving a linear system. Otherwise, the weights can be tuned so that a measure of similarity between the deforming image and the target image is optimized. Continuum-mechanical models, (b), can also be used to compute these deformation fields (Davatzikos et al., 1996; Christensen et al., 1996; Gee et al., 1998; Thompson et al., 2000; Miller et al., 2002). These models describe how real physical materials deform. Different choices of the Lamé elasticity coefficients, λ and μ, in the Cauchy-Navier equations (shown in continuous form, (b)) result in different deformations, even if the applied internal displacements are the same. For brain image transformations, values of elasticity coefficients can be chosen to limit the amount of curl (*middle right*) in the deformation field. (*Note*: To help visualize differences, displacement vector fields have been multiplied by a factor of 10, but the elasticity equations are valid only for small deformations). (c) shows the complexity of a typical deformation field, in this case one used to reconfigure a histologic section stained for molecular content. Curve and surface anatomic landmarks are used to constrain the mapping, and the Cauchy-Navier equations are solved to estimate how the rest of the 3D volume deforms. [Panel (a) is *adapted from Davis et al., 1997*].

Fig. 18. *Tensor Maps of Local Volumetric Loss in Normal Elderly Individuals*. Local volume loss patterns in the hippocampus of an elderly subject (here, over a 6 month interval) are hard to appreciate from raw MRI data (*left*). They can be localized by using 3D surface models to drive a 3D continuum-mechanical partial differential equation (PDE; see Fig. 17) from which dynamic statistics of loss are derived. Comparison and averaging of this loss rate data across subjects requires a second PDE to convect the attribute data onto an average neuroanatomical atlas (*final 4 panels*; Evans *et al.*, 1994; see Thompson *et al*., 1997, 2000, 2001 for methods and applications).

Fig. 19. *Correlation between Twins in Gray Matter Distribution*. Genetically identical twins are almost perfectly correlated in their gray matter distribution, with near-identity in frontal (F), sensorimotor (S/M) and perisylvian language cortices. Fraternal twins are significantly less alike in frontal cortices, but are 90-100% correlated for gray matter in perisylvian language-related cortex, including supramarginal and angular territories and Wernicke's language area (W). The significance of these increased similarities, visualized in color, is related to the local intraclass correlation coefficents (r), and can be transformed into maps of heritability and genetic influences on brain structure (Thompson et al., 2001; Plomin and Kosslyn, 2001).

Fig. 20. *Creating Brain Maps and Anatomical Models*. An image analysis pipeline (Thompson et al., 2001) is shown here. It can be used to create maps that reveal how brain structure varies in large populations, differs in disease, and is modulated by genetic or therapeutic factors. This approach aligns new 3D MRI scans from patients and controls (1) with an average brain template based on a population (here the ICBM template is used, developed by the International Consortium for Brain Mapping [39]). Tissue classification algorithms then generate maps of gray matter, white matter and CSF (2). To help compare cortical features from subjects whose anatomy differs, individual gyral patterns are flattened (3) and aligned with a group average gyral pattern (4). If a color code indexing 3D cortical locations is flowed along with the same deformation field (5), a crisp group average model of the cortex can be made (6), relative to which individual gyral pattern differences (7), group variability (8) and cortical asymmetry (9) can be computed. Once individual gyral patterns are aligned to the mean template, differences in gray matter distribution or thickness (10) can be mapped, pooling data from homologous

regions of cortex. Correlations can be mapped between disease-related deficits and genetic risk factors (11). Maps may also be generated visualizing linkages between deficits and clinical symptoms, cognitive scores, and medication effects.

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